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## ROLE OF BLOOD PRESSURE IN THE DEVELOPMENT OF CONGESTIVE HEART FAILURE

### The Framingham Study

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**Abstract** A representative population sample of 5192 men and women was followed for 16 years, during which overt congestive heart failure (CHF) developed in 142. In the age range from 30 to 62 years the dominant etiologic precursor was hypertension, which preceded CHF in 75 per cent of the cases. Six times more CHF developed in hypertensive than in normotensive persons.

Examination of the association of myocardial hypertrophy on x-ray or electrocardiographic study with systolic versus diastolic pressure revealed little to suggest a greater role for diastolic pressure. Systolic and diastolic pressure together, mean arterial pressure, pulse

pressure, and tension-time index discriminated potential hypertrophy and CHF no better than systolic pressure alone. Examination of the correlation of heart weight and left ventricular thickness at autopsy with premorbid systolic versus diastolic pressure revealed a better correlation with systolic than with diastolic pressure.

CHF was a lethal phenomenon, with only 50 per cent surviving for five years. Early, vigorous and sustained control of elevated blood pressure — systolic as well as diastolic — appears the chief means for preventing CHF in the general population.

**S**TUDY of the evolution of congestive heart failure (CHF) in the general population in Framingham has revealed it to be a potent force of mortality. The dominant precursor as it occurs in the general population is hypertension, which preceded 75 per cent of the cases.<sup>1</sup> Despite modern management, CHF proved extremely lethal, with a 50 per cent mortality within five years of diagnosis — a death rate seven times that of the general population.<sup>1</sup>

In view of the dominant role of hypertension and evidence that its control can indeed delay the onset of CHF and mortality from it,<sup>2-4</sup> a more detailed examination of the role of hypertension in the development of CHF was undertaken.

### METHODS

The Framingham study was implemented in 1949 to examine the epidemiology of cardiovascular disease in a general population sample. Since its inception 5209 men and women 30 to 62 years of age at entry have been followed biennially for the development of cardiovascular disease. Detailed descriptions of the sampling procedure, response rate, methods of examination and criteria employed have been presented else-

where.<sup>5-6</sup> At each biennial examination each subject received a detailed cardiovascular survey that included history and physical examination, 13-lead electrocardiogram, chest x-ray study, and vital-capacity, hemoglobin and a variety of blood chemical determinations.

### Criteria

Upon completion of each biennial examination a diagnosis of CHF was entertained on clinical grounds, chest x-ray findings and total vital capacity. Persons who were suspected of having cardiac failure were seen by a second medical examiner so that two opinions could be obtained. Furthermore, the records of those suspected of having CHF on biennial heart-clinic examination, interim information from hospital records, or reports from physician's offices were reviewed by a panel of investigators using uniform criteria to provide a consistent diagnosis of known specifications. The criteria employed have previously been reported.<sup>1</sup> Only those classed as having definite CHF by these criteria are included in this analysis, excluding those who had CHF at entry to the study.

After persons who met criteria for CHF at the time of initial examination were excluded there were 5192 men and women at risk of a first CHF event over the ensuing 16 years. Follow-up observation was reasonably complete, with only 2 per cent completely lost. Of those who took the ninth examination, 84 per cent received every possible biennial examination; the rest were seen at less regular intervals. Admissions to the

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only general hospital in the town were monitored daily.

Three blood-pressure measurements were obtained on each subject during the biennial examination — two by the examining physician, and the other by the nurse. All were casual and obtained with the subject seated. For analysis of pressure per se the first determination obtained by the examining physician — which was in general higher than the second — was used. "Hypertension" is arbitrarily defined as two systolic pressures of 160 mm of mercury or greater or two diastolic pressures of 95 mm or higher. Normotension is defined as both systolic pressures below 140, and both diastolic pressures below 90 mm of mercury.

Incidence rates for CHF were determined in the population at risk classified for systolic and diastolic pressure and "hypertensive status," as judged by the first examiner. To assess the joint effect of related variables, coefficients of a multivariate logistic risk function were estimated with the use of the discriminant-function method<sup>7</sup> or the maximum-likelihood method.<sup>8</sup>

## RESULTS

In the 16 years of follow-up observation definite evidence of CHF according to the specified criteria developed in 81 men and 61 women. The 16-year incidence increased precipitously with age, with a modest male predominance.<sup>1</sup> However, in both young and old, risk was markedly influenced by antecedent hypertensive status. Analysis of the relation of blood-pressure status to risk of CHF at each biennial examination revealed the risk for hypertensive patients to be six times that for normotensive persons (Table 1). Hypertension not only was a potent contributor to CHF incidence but also was the most common factor in the background of victims of CHF as it occurred in the general population.<sup>1</sup> Fully 75 per cent of those who acquired CHF during the 16-year period had prior hypertension.

### Systolic versus Diastolic Pressure

An examination of the risk of CHF in the population classified at each biennial examination according to their systolic versus their diastolic pressures reveals little to suggest a stronger relation to the diastolic component. Comparison of the smoothed curves of incidence of CHF according to antecedent systolic versus diastolic pressures (with the scales of measurement made comparable by their expression in terms of the number of standard deviations from the means of their distributions) reveals slopes that are actually steeper for systolic pressure (Fig. 1A and B). Comparison of the computed regressions of incidence of CHF on systolic (B, or regression coefficient in discriminant function, equal to 0.648) versus diastolic pressure (B equal to 0.466) in men standardized for the different range of values, and averaged over the three 10-year age groups, reveals no hint of a more pronounced relation to diastolic pressure. The same reservation applies in women (0.688 vs. 0.611). If there is any utility of one over the other, systolic would appear the better choice. Furthermore, both components of the pressure together and the mean arterial pressure discriminated potential cases of CHF no better than systolic pressure alone. This was also true for coronary heart disease and stroke, frequent concomitants of CHF that share its precursors.<sup>9,10</sup>

### Modified Tension-Time Index

The product of the arterial pressure and heart rate has been singled out as the chief hemodynamic determinant of the myocardial oxygen uptake of the ejecting ventricle.<sup>11,12</sup>

In the Framingham experience the product of systolic blood pressure and pulse rate was no better a predictor of CHF than systolic pressure alone, although it was a considerable improvement over pulse rate alone (Table 2). An examination of the regressions of pulse rate, systolic blood pressure and their product on incidence of CHF reveals that taken together all are strongly related to CHF in multivariate analysis. In

Table 1. Incidence of CHF According to Hypertensive Status at Examination and According to Sex and Age.\*

AGE AT EXAMINATION	PERSON-YR AT RISK AT EXAMINATION			INCIDENCE IN EXAMINATION INTERVAL			AVERAGE ANNUAL RATE/10,000			RELATIVE RISK
	TOTAL	NORMAL	HYPERTENSION	TOTAL	NORMAL	HYPERTENSION	TOTAL	NORMAL	HYPERTENSION	
Men:										
35-44	16,814	8,586	2,964	80	13	45	24	8	76	7.9†
45-54	4,568	2,701	522	4	0	3	4	0	29	
55-64	6,321	3,272	1,100	24	3	15	19	5	68	14.9
65-74	4,539	2,061	1,020	35	8	19	39	19	93	4.8
	1,386	552	322	17	2	8	61	18	124	6.9
Women:										
35-44	21,426	11,181	4,013	61	12	36	14	5	90	4.2†
45-54	5,627	4,277	331	4	3	0	4	4	0	
55-64	7,907	4,370	1,226	10	4	3	6	5	12	2.7
65-74	5,956	2,087	1,726	32	4	22	27	10	64	6.7
	1,936	447	730	15	1	11	39	11	75	6.7

\*Source: Table 11-18-B of Section 26 of the monograph by Shurtleff D: Some Characteristics Related to the Incidence of Cardiovascular Disease and Death: the Framingham Study: an epidemiological investigation of cardiovascular disease. Bethesda, Maryland, National Heart Institute, 1970, Section 26.

†Age-adjusted by indirect method using as standard rates the sex-age-specific incidence rates for the entire study.

population, according to reveals little coincidence as diastolic made com- number of distribu- or systolic computed, or regres- (r equal to 0.648) men stan- averaged hint of a sure. The 0.611). If systolic would h compon- n arterial (If no bet- o true for concomi-

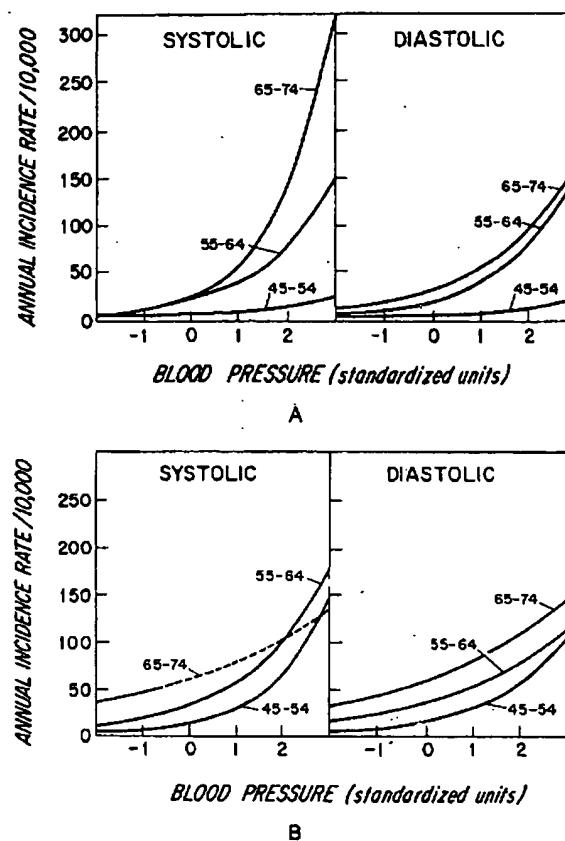


Figure 1. Smoothed Average Annual Incidence Rate for CHF According to Blood Pressure, by Age for Men (A) and for Women (B), Framingham Heart Study, at 16-Year Follow-up Examination.

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discriminant analysis both systolic blood pressure and the product of pulse rate and systolic pressure have a strong univariate relation to incidence of CHF, whereas pulse rate itself is significantly related in some age groups but not others (Table 2). Since the product of pulse rate and systolic pressure is strongly correlated with systolic pressure ( $r$  equal to 0.7 to 0.8) it is difficult to separate their contributions by multivariate analysis. However, a bivariate regression with systolic pressure reduces the contribution of pulse rate to incidence of CHF to near zero.

#### CARDIAC ENLARGEMENT

Dilatation and hypertrophy are cardinal features of CHF. Increase in cavity size and increased bulk of the myocardium can be detected clinically by chest x-ray study for cardiac enlargement and by electrocardiography for left ventricular hypertrophy. A common precursor of both dilatation and hypertrophy is hypertension. An examination of the prevalence of cardiac enlargement on the x-ray film reveals that it is indeed strikingly related to the blood-pressure level (Fig. 2). However, the prevalence of cardiac enlargement on x-ray study was no more closely related to diastolic than to systolic pressure.

Electrocardiographic evidence of left ventricular hy-

Table 2. Significance of Systolic Blood Pressure (SBP), Pulse Rate (PR) and Their Product (SBP  $\times$  PR) as Discriminators of CHF.

AGE AT 1ST EXAMINATION	MEN		WOMEN	
	CHI-SQUARE	DEGREES OF FREEDOM	CHI-SQUARE	DEGREES OF FREEDOM
35-44:				
SBP	(n = 16)*	1	0.49	1
PR	0.47	1	0.40	1
SBP $\times$ PR	13.18	1	0.50	1
Generalized distance				
SBP, PR	37.46	2	0.70	2
SBP, SBP $\times$ PR	37.47	2	0.56	2
SBP, PR, SBP $\times$ PR	37.47	3	1.88	3
45-54:				
SBP	(n = 33)*	1	48.20	1
PR	2.50	1	8.25	1
SBP $\times$ PR	17.56	1	46.43	1
Generalized distance				
SBP, PR	24.55	2	50.39	2
SBP, SBP $\times$ PR	24.73	2	52.58	2
SBP, PR, SBP $\times$ PR	27.54	3	61.69	3
55-62:				
SBP	(n = 28)*	1	7.50	1
PR	7.05	1	3.10	1
SBP $\times$ PR	16.00	1	9.28	1
Generalized distance				
SBP, PR	14.25	2	8.97	2
SBP, SBP $\times$ PR	16.03	2	9.67	2
SBP, PR, SBP $\times$ PR	20.03	3	11.56	3

\*CHF incidence.

<sup>†</sup>Measure of the degree of dissimilarity of the 2 populations with respect to the independent variable (or variables) described.

hypertrophy also was strikingly related to blood pressure, systolic as much as diastolic (Fig. 2). Both these hypertensive cardiac manifestations were as strongly related

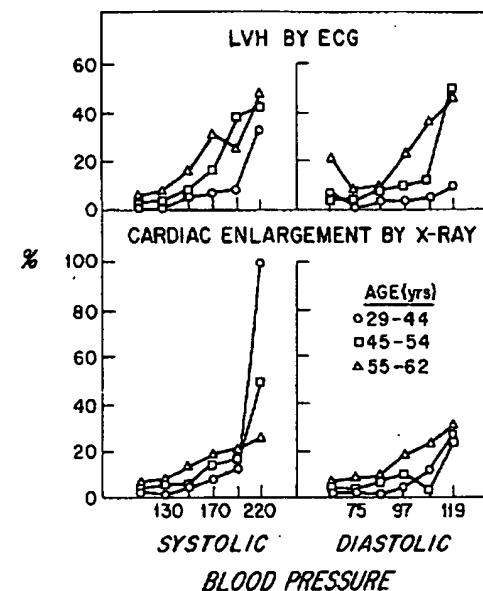


Figure 2. Prevalence of Left Ventricular Hypertrophy by Electrocardiographic or Cardiac Enlargement by X-Ray Criteria According to Initial Systolic and Diastolic Blood Pressure in Men, 30-62 Years of Age at Entry into Framingham Study.

to systolic as to diastolic pressure. The higher the pressure, the more likely was a person to have or to acquire electrocardiographic evidence of hypertrophy until at pressures of 200 mm of mercury or more, 58 per cent manifested it within 12 years.<sup>13</sup> However, x-ray and electrocardiographic findings of cardiac enlargement may reflect different phenomena. Only 35 per cent of men and 50 per cent of women 45 to 64 years of age with left ventricular hypertrophy apparent on electrocardiography had concurrent evidence of cardiac enlargement on x-ray examination.<sup>13</sup>

Analysis of autopsy specimens at Framingham reveals that some attributes measured nine years before death in the preterminal state are related to heart weight. Of these, relative body weight and blood pressure appear to be the chief determinants of myocardial thickness and cardiac weight. Again, there is little evidence that the net effect of diastolic pressure exceeds that of systolic as judged by the size of the correlation coefficients (Table 3).

Table 3. Correlation of Heart Weight and Thickness at Autopsy on 66 Men and 44 Women with Age at Death and with Blood Pressure, Relative Weight and Cholesterol Measured Nine Years before Death.

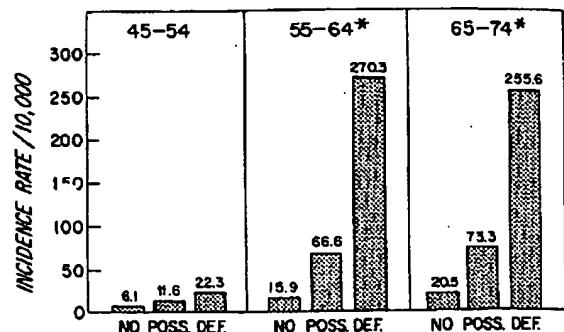
CARDIAC STATUS	CORRELATION COEFFICIENTS				
	AGE AT DEATH	FRAMINGHAM RELATIVE BODY WEIGHT	SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE	CHOLESTEROL
<b>Men:</b>					
Heart weight	-.073	.343*	.181	.039	.164
Left ventricular muscle thickness	-.068	.277†	.253†	.084	.264†
<b>Women:</b>					
Heart weight	.249	.423*	.418*	.381†	.084
Left ventricular muscle thickness	.315†	.291	.397*	.353†	.078

\*Significant at 0.01 level. —

†Significant at 0.05 level.

#### Left Ventricular Hypertrophy and CHF

Electrocardiographic evidence of left ventricular hypertrophy in the Framingham cohort was strongly associated with both hypertension and coronary disease.<sup>13</sup> Persons with definite evidence (including ST-segment and T-wave abnormality as well as increased voltage) were extremely vulnerable to CHF. Persons with "possible" evidence of hypertrophy (mainly voltage abnormality) had a moderately increased risk. Those with "definite" evidence had about 10 times the risk of those without any abnormality (Fig. 3A and B). The markedly increased risk of CHF associated with electrocardiographic evidence of left ventricular hypertrophy probably reflects the severity and duration of predisposing hypertension and the compensatory cardiac hypertrophy. It could also reflect ischemic myocardial involvement due to associated accelerated coronary atherosclerosis. Whatever the explanation, hypertensive heart disease with electrocardiographic manifestation of left ventricular hypertrophy is an ominous harbinger of CHF.

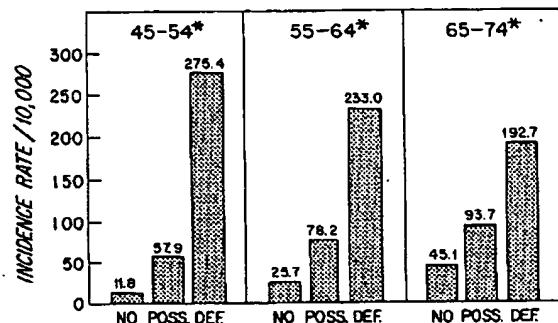


LEFT VENTRICULAR HYPERTROPHY EACH BIENNIAL EXAM

\*Trend is Statistically Significant at  $p < 0.05$  Level

Source: Framingham Monograph 26

A



LEFT VENTRICULAR HYPERTROPHY EACH BIENNIAL EXAM

\*Trend is Statistically Significant at  $p < 0.05$  Level

Source: Framingham Monograph 26

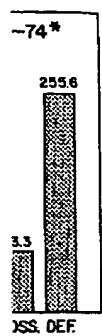
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Figure 3. Smoothed Average Annual Incidence of CHF (at 16-Year Follow-up Examination) According to Electrocardiographic Evidence of Left Ventricular Hypertrophy in Women (A) and in Men (B) 45-74 Years of Age.

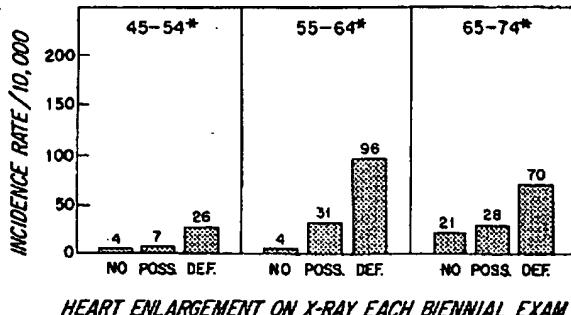
#### Heart Enlargement on X-Ray Study and CHF

Hypertension is a prominent cause of cardiac enlargement as seen on x-ray examination. Cardiac enlargement is a hallmark of CHF. Risk of CHF in persons free of overt evidence of CHF was decidedly increased, the risk increasing with the degree of enlargement (Fig. 4A and B). Since cardiac enlargement was one of the criteria for CHF, this to some extent is a self-fulfilling prophecy.

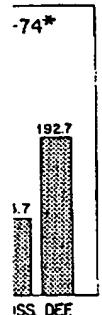
Increased blood pressure, cardiac enlargement, electrocardiographic manifestations of left ventricular hypertrophy and coronary heart disease are inter-related findings apt to coexist in adult populations. It is thus difficult to disentangle the net effect of each in the development of CHF. An examination of the regression of incidence of the disease on systolic blood pressure in multivariate analysis (standardized for the different units of measurement) allows an assessment of the net effect of systolic pressure, taking into account the other variables (Table 4). As judged by the size of the



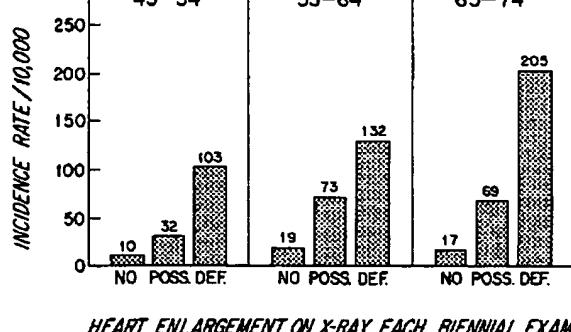
INITIAL EXAM

\*Trend is Statistically Significant at  $p < 0.01$  Level

Source: Framingham Monograph 26



INITIAL EXAM

\*Trend is Statistically Significant at  $p < 0.01$  Level

Source: Framingham Monograph 26

B

Figure 4. Average Annual Incidence of CHF (at 16-Year Follow-up Examination) According to Heart Enlargement on X-Ray Study in Women (A) and in Men (B) 45-74 Years of Age.

standardized regression coefficients, the net contribution of systolic pressure is as great as that of coronary heart disease, x-ray enlargement, and electrocardiographic evidence of left ventricular hypertrophy. The slightly greater coefficients for cardiac enlargement on x-ray study are no doubt accounted for in part by the use of this finding as a criterion for CHF. The multivariate regression coefficients for systolic pressure are reduced by half as compared to the univariate coefficients, suggesting that a good deal of the blood-pressure association with CHF may be explained by the coexisting enlargement of the heart, and myocardial ischemia. This is, of course, a not unreasonable pathogenetic mechanism for the action of systolic pressure in producing CHF. As might be expected risk of CHF associated with any degree of high blood pressure is enhanced when cardiac enlargement or coronary heart disease appears.

#### DISCUSSION

Examination of the etiologic precursors of CHF as it occurs in the general population, undistorted by the selective bias of hospital-admission practices or vary-

Table 4. Standardized Multivariate Regression Coefficients\* of CHF on Systolic Blood Pressure and Heart Impairment.

AGE	INCIDENCE OF CHF	SYSTOLIC BLOOD PRESSURE	HEART ENLARGEMENT BY X-RAY STUDY	LEFT VENTRICULAR HYPERTROPHY BY ELECTROCARDIOGRAM	CORONARY HEART DISEASE
<b>Men:</b>					
45-54	24	0.5249	0.4793	0.2718	0.3074
55-64	35	0.3474	0.3584	0.2935	0.4233
65-74	17	0.0545	0.6716	0.1936	0.4587
Average (45-74)					
6		0.3704	0.4497	0.2704	0.3752
SE (6)		0.0995	0.0898	0.0669	0.0702
Ratio: 6/SE (6)		3.72	5.01	4.04	5.35
<b>Women:</b>					
45-54	10	0.3765	0.4829	-0.678	0.1883
55-64	32	0.3127	0.6790	0.3735	0.1798
65-74	15	0.6086	0.1569	0.3757	0.4439
Average (45-74)					
6		0.3864	0.5073	0.3088	0.2350
SE (6)		0.1064	0.1377	0.0807	0.0747
Ratio: 6/SE (6)		3.63	3.69	3.83	3.15

\*Coefficients are obtained for multiple logistic function by the method of Duncan-Walker. Indicating the coefficient in the  $i$ th age group of a variable by  $b_i$  & its variance by  $V(b_i)$ , the average of the 3 age groups & the standard error of this average are:

$$\bar{b} = \frac{\sum b_i / V(b_i)}{\sum 1 / V(b_i)}$$

$$SE(\bar{b}) = \sqrt{\frac{1}{\sum 1 / V(b_i)}}$$

ing criteria, reveals hypertension to be the salient feature before failure in 75 per cent of the victims of myocardial decompensation. CHF, as defined, was an extremely lethal process; 60 per cent of the men and 40 per cent of the women died within five years of onset (Table 5). This is an average annual death rate about seven times that of persons without CHF.<sup>1</sup> An appalling prognosis was noted for this group of predominantly hypertensive patients with CHF, even if those with established coexisting coronary heart disease are excluded. As many as 20 per cent of the men and 14 per cent of the women died within a year of diagnosis (Table 5).

It is clear that a prophylactic approach is indicated and that the key to this is the early, vigorous and sustained control of hypertension. A better understanding of the details of the relation of blood pressure to the development of CHF should contribute to more efficient prophylaxis against this lethal end stage of heart disease. Little direct evidence can be cited in support of

Table 5. Probability of Death in Interval after First Occurrence of Congestive Heart Failure.

YR AFTER EVENT	MEN		WOMEN	
	TOTAL	WITHOUT CORONARY HEART DISEASE*	TOTAL	WITHOUT CORONARY HEART DISEASE*
1	.205	.205	.140	.129
3	.452	.436	.320	.355
5	.615	.584	.433	.427
7	.707	.735	.603	.559
9	.819	.841	.691	.685

\*Subjects with prior or coexisting coronary heart disease eliminated from population at risk of death.

the concept that the cardiac sequelae of essential hypertension derive principally from the diastolic component of the blood pressure and that it is meddlesome to over-react to the level of systolic blood pressure. A systematic examination of the relation of each component of the blood pressure to the occurrence of cardiac hypertrophy on x-ray study, electrocardiography or autopsy and to the development of CHF reveals nothing to suggest a more potent role for diastolic pressure. The surprising failure of diastolic pressure to predict CHF better than systolic pressure may in part be due to the greater inaccuracy in measurement of diastolic pressure and the narrower range of values for this component of the pressure.

With advancing age a widening of the pulse pressure, with a disproportionate rise in systolic pressure owing to a loss of elasticity of the large arteries, is characteristic. This is believed to be an innocuous phenomenon and not true "hypertension." Since there is no evidence of a declining influence of blood pressure in general and systolic pressure in particular on the cardiac sequelae of hypertension with advancing age this concept must be questioned.<sup>9,10,14,15</sup>

The evil consequences of myocardial hypertrophy induced by hypertension (which often culminates in failure) requires further explanation. Hypertensive hypertrophy appears to differ from other types, which are associated with improved cardiac performance. Perhaps the associated accelerated coronary atherosclerosis also promoted by hypertension explains the poor performance in hypertensive hypertrophy. The increased pressure load imposed on the heart is evidently well tolerated for decades. It is only when the increased muscle mass can no longer cope with the load — perhaps owing to presbycardia or more likely the progressive myocardial ischemia imposed as coronary vessels begin to shut down — that myocardial insufficiency develops.

The concept of relative ischemia was proposed by Fishberg<sup>16</sup> to explain hypertensive CHF as coronary flow fails to keep pace with the increased demands of the hypertrophied myocardium. That this concept is in fact valid remains to be established.<sup>17</sup> It has also been suggested that compression of intramural vessels by the hypertrophied myocardium may interfere with flow.<sup>18</sup>

Except when there is a defect in atrioventricular conduction, the tension-time index should be a better prognosticator of cardiac hypertrophy, dilatation and CHF in hypertensive patients than the level of systolic pressure alone. The failure to corroborate this hypothesis could stem from the fact that the blood pressures were casual values. Perhaps if the pressures and pulse rates were obtained under basal conditions or a standardized load the tension-time index might better reflect the pressure workload of the heart and the heart's ability to cope with its workload. It is also possible that the high correlation between tension-time index and the systolic pressure precludes the possibility of demonstrating the efficiency of one as compared to the other.

Few risk factors in coronary, hypertensive cardiovascular, and cerebrovascular disease are more easily detected and readily controlled than hypertension. Misconceptions may exist concerning the nature and consequences of hypertension that tend to impede its effective prophylactic management. Elevated blood pressure, whether predominantly systolic or diastolic, in either sex, at any age, deserves attention.<sup>14,15</sup> Moderately elevated diastolic pressures appear more serious when accompanied by pronounced systolic elevations than when accompanied by only modest systolic elevations. Hypertension assumes grave importance when attended by cardiac enlargement, electrocardiographic evidence of LVH (or a falling vital capacity) even though the subject may be asymptomatic at the time.

To await the onset of symptoms or evidence of target-organ involvement before treating hypertension seems imprudent. It has been convincingly demonstrated that vigorous management of moderate and severe hypertension does in fact delay failure and early mortality.<sup>2-4</sup> In view of the serious prognosis once failure develops it seems ill advised to await signs of it before proceeding to control the blood pressure. Consideration should also be given to the possibility that hypertensive persons with electrocardiographic evidence of left ventricular hypertrophy or x-ray enlargement of the heart may benefit from glycosides before the onset of overt failure if noninvasive procedures (e.g., systolic-time intervals, diminishing vital capacity, a rapid pulse response to moderate exertion and a rapidly enlarging heart) suggest impaired cardiac function. Proof that glycosides employed in these circumstances will delay onset of overt failure and prolong survival is lacking. Efforts to assess this hypothesis seem long overdue.

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## FAMILIAL THYMIC APLASIA

### Attempted Reconstitution with Fetal Thymus in a Millipore Diffusion Chamber

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MARIANNE SCHUELEIN, M.D., HEINZ BAUER, M.D., AND JOSEPH A. BELLANTI, M.D.

**Abstract** A 10-week-old female infant with familial congenital thymic aplasia without delayed hypersensitivity to common skin-test antigens underwent fetal-thymus implantation. Six hours after the implantation of a fetal thymus enclosed in a Millipore chamber phytohemagglutinin responsiveness was demonstrable in

the patient's peripheral lymphocytes. The infant's death of aspiration pneumonia nine days after implantation did not allow evaluation of the extent of the immunologic reconstitution. Thymic-cell immunologic function can be induced in man with fetal-thymus humoral factors.

**CONGENITAL** absence of the thymus and parathyroid glands was first fully appreciated as a distinct clinical syndrome in 1965.<sup>1</sup> The apparent etiology is a failure of embryonic development of the third and fourth pharyngeal pouches, the anlage of the thymus and parathyroid glands. No hereditary predisposition has previously been described. Affected infants become symptomatic shortly after birth, exhibiting hypocalcemic tetany or convulsions and severe retardation of growth and development. Later in infancy they manifest an increased clinical severity with infectious agents that are normally handled through cell-mediated responses (e.g., monilia). Therefore, early recognition of the disorder is imperative since immunization with live vaccines may be fatal.

Recent reports demonstrate that the implantation of fetal thymus tissue into these patients restores cell-mediated immune function<sup>2-4</sup>; fetal tissue was used to minimize the risk of a graft-versus-host reaction. The use of thymus tissue in Millipore diffusion chambers or purified thymic extract for thymectomized animals has resulted in at least partial reconstitution.<sup>5-7</sup> Such methods decrease greatly the risk of the graft-versus-host reaction; application to treatment of immune deficiencies in the clinical setting is therefore apparent.

### CASE REPORT

A Caucasian female infant weighed 3.3 kg. at birth; the initial physical examination was described as unremarkable. The 29-year-old mother's only other pregnancy was by a previous marriage and resulted in the birth of a male infant who died at 4 months of age.

The patient's 3-day nursery course was uneventful, but the mother noted difficulty with feeding and frequent "spitting-up" shortly after returning home. At 3 to 6 days of age "twisting and jerking" motions of the extremities were observed. At 12 days of age the patient had 2 generalized seizures and was subsequently referred to Georgetown University Hospital. Physical examination demonstrated a lethargic infant with generalized depression of neurologic function, hypertelorism, and slightly low-set ears without malformation of the pinnae. A thymic shadow was not observed on routine chest roentgenograms. Other abnormal laboratory values included a serum calcium of 6.2 to 7.4 and a phosphorus of 5.5 to 8.0 mg per 100 ml.

Initial immunologic studies revealed white-cell counts of 13,500 to 17,600, absolute neutrophil counts of 1500 to 3520 and absolute lymphocyte counts of 4050 to 6160 per cubic millimeter. Total complement activity and  $\beta 1c-1a$  globulin concentrations were within normal limits. Serial quantitative immunoglobulin determinations at 3, 6 and 12 weeks were within normal limits for age. A maximum flagellar (H) agglutination titer increased from less than 1:2 to 1:80 14 days after stimulation with typhoid vaccine,\* agglutinins to somatic (O) antigen were not detected. An excisional biopsy of right inguinal lymph nodes was obtained 12 days after intradermal injection of 0.4 ml of typhoid vaccine into the right medial thigh. Attempts to stimulate peripheral blood lymphocytes in vitro with phytohemagglutinin (PHA) and pokeweed mitogen elicited almost no response (Table 1). Intradermal injection of 1  $\mu$ g and 2  $\mu$ g of PHA resulted in no induration or erythema at the site of injection.

The hospital course was relentlessly downhill. Hypocalcemia was initially treated with intramuscular parathyroid hormone and subsequently with oral vitamin D. However, wide fluctuations of serum calcium levels made management difficult. A peripheral blood eosinophil count of 41 to 49 per cent was noted. Growth remained severely retarded, and at 10 weeks the weight was 3.2 kg; she refused

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\*Typhoid vaccine, U.S.P., Eli Lilly Co., Indianapolis, Ind.

## Original Contributions

# Systolic Blood Pressure, Arterial Rigidity, and Risk of Stroke

### The Framingham Study

William B. Kannel, MD; Philip A. Wolf, MD; Daniel L. McGee, PhD; Thomas R. Dawber, MD; Patricia McNamara; William P. Castelli, MD

• Based on prospective data from the Framingham study relating systolic pressure, diastolic pressure, age, and pulse-wave configuration to future stroke incidence, it would appear that isolated systolic hypertension predisposes to stroke independent of arterial rigidity. The prevalence of isolated systolic hypertension increased with age and with the degree of blunting of the dicrotic notch in the pulse wave. Subjects with isolated systolic hypertension experienced two to four times as many strokes as did normotensive persons. While diastolic pressure is related to stroke incidence, in the subject with systolic hypertension, the diastolic component adds little to risk assessment and in men, in this subgroup, appears unrelated to stroke incidence.

(JAMA 1981;245:1225-1229)

EPIDEMIOLOGIC investigations have served to emphasize the importance of hypertension as a contributor to cardiovascular disease in general and to stroke in particular.<sup>1-4</sup> Because hypertension is the predominant contributor to stroke, a detailed examination of the role of blood pres-

sure (BP) in the evolution of cerebrovascular disease is warranted.

Previous studies of the problem in

#### For editorial comment see p 1250.

Framingham (Mass) have established elevated BP in general and systolic pressure in particular as a predictor of stroke incidence.<sup>5</sup> This report examines the role of isolated systolic hypertension in the development of cerebrovascular disease and attempts to assess its effect taking arterial rigidity into account.

#### METHODS

In the Framingham study a cohort of 5,209 men and women aged 30 to 62 years

when the study originated in 1948 has been followed up biennially for the development of cardiovascular disease, including strokes. Data are available for analysis of 24 years of follow-up of stroke incidence in relation to antecedent BP status.

The criteria employed for the diagnosis of stroke and the methods of investigation have been published elsewhere in detail.<sup>6</sup> The stroke entity identified includes the following: atherothrombotic brain infarction, transient ischemic attacks, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral embolus.<sup>7</sup> Since in the Framingham cohort, all varieties of stroke have been shown to be related to hypertension, this analysis makes no attempt to separate the strokes by type. Minimum criteria for a stroke consisted of a focal neurological deficit of abrupt onset lasting more than 24 hours without other explanation. Subjects were often examined at the time of hospitalization and subsequently in the Framingham study clinic by a qualified neurologist (P. W.) assigned to the study. Each new case was verified by a review panel of physicians, including a neurologist.

Blood pressures were determined with patients seated with their left arm on a desk at heart level using a mercury sphygmomanometer with a bladder large enough to encircle an obese arm. Three pressures were reported on each subject, two by a physician and one by a nurse. Isolated systolic hypertension was defined

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Reprint requests to 118 Lincoln St, Framingham, MA 01701 (Dr Castelli).

as a systolic pressure of 160 mm Hg or greater accompanied by diastolic pressures under 95 mm Hg.

Pulse-wave recordings were obtained with an oscillometric device (Vasculograph) in the upper extremity using a narrow cuff applied to the finger.<sup>14</sup> Using the method described by Lax et al<sup>1</sup> and the instrument they provided the Framingham study during 1965 and 1966, pulse-wave recordings were made on 1,825 consecutive subjects,<sup>1</sup> from tracings obtained as the pressure was raised to above the diastolic. The depth of the dicrotic notch was graded from absent (4) to pronounced (1) from the tracing that showed maximum notching—usually just below the diastolic pressure (Fig 1). Readable tracings were obtained on 1,778 subjects (980 female and 798 male). Hypertensive subjects were routinely referred to their physicians, but until 1956 there were no convenient oral antihypertensive agents available, and even after this time, until recently there was a gross undertreatment.<sup>15</sup> Also, most physicians judged the need for treatment on the basis of the diastolic rather than the systolic BP.

The contributions of systolic and diastolic pressures and pulse-wave configuration to the occurrence of strokes were determined by estimating standardized logistic coefficients for regression of stroke incidence on these variables and age.<sup>16</sup>

The follow-up of the cohort over the 24 years was reasonably complete with about 85% taking each clinical examination and only 2% lost to follow-up for death. Hospital admissions for suspected strokes were monitored daily in the only hospital in town.

## RESULTS

Over 12 years of follow-up, of 668 men and 835 women who had satisfactory pulse-wave recordings and diastolic pressures under 95 mm Hg at time of the eighth examination (1965 to 1966) and were free of cardiovascular disease, 44 men and 41 women experienced strokes.

An examination of the prevalence of isolated systolic hypertension in relation to the depth of the dicrotic notch in the pulse-wave recording showed a distinct trend in men and a distinct excess in those women with absent dicrotic notches (Table 1). Mean systolic pressure also increased with blunting of the incisura but only in men aged 65 to 74 years (Table 2).

The risk of strokes over the entire 24 years of follow-up was strikingly related to the level of systolic pressure in subjects with diastolic pres-

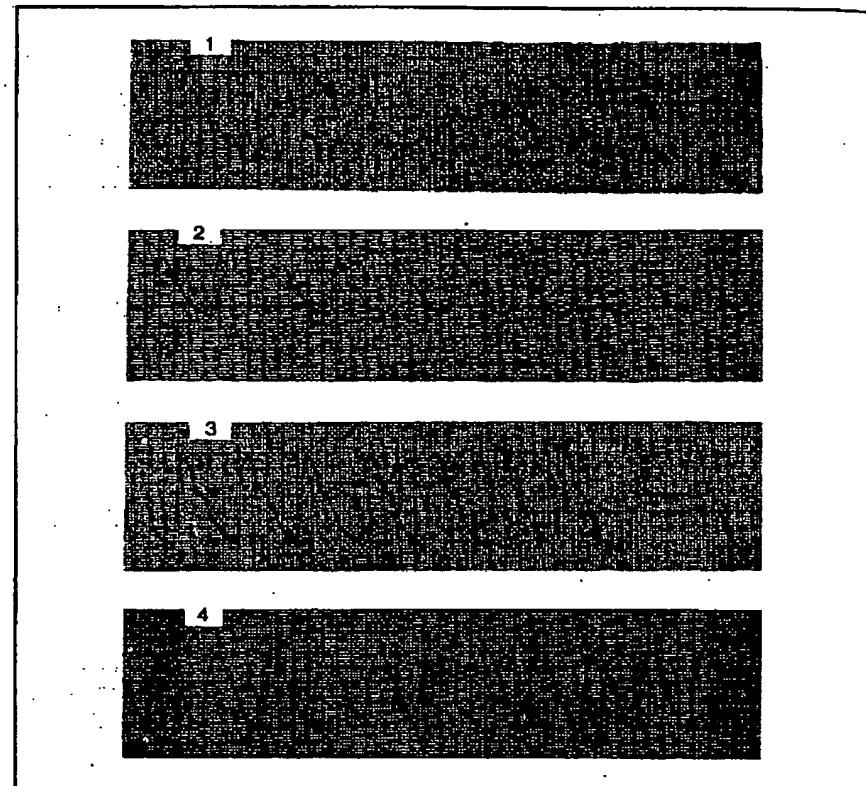


Fig 1.—Vasculography. Classes 1 to 4 depending on prominence of the dicrotic notch (from Dawber et al<sup>1</sup>).

Table 1.—Age-Adjusted Mean Pulse Pressure and Prevalence of Isolated Systolic Hypertension\*

Age Group, yr	Men		Women		Men		Women		Men		Women	
	1	2	1	2	1	2	1	2	1	2	1	2
45-54	122.5	122.5	124.6	124.6	121.2	121.2	124.4	124.4	120.5	120.5	122.0	122.0
55-64	122.1	122.1	124.5	124.5	121.2	121.2	124.4	124.4	120.5	120.5	122.0	122.0
65-74	122.1	122.1	124.5	124.5	121.2	121.2	124.4	124.4	120.5	120.5	122.0	122.0
75-84	122.1	122.1	124.5	124.5	121.2	121.2	124.4	124.4	120.5	120.5	122.0	122.0
85-94	122.1	122.1	124.5	124.5	121.2	121.2	124.4	124.4	120.5	120.5	122.0	122.0

\*By level of pulse-wave recording for men and women aged 45 to 74 years.

†Depth of dicrotic notch, 4 equals absent; 1 equals pronounced.

sures below 95 mm Hg. This persisted on age-adjustment and appeared to be more striking in men both on a relative and absolute scale. In subjects with an elevated systolic pressure, on the other hand, the risk was not related at all to the accompanying diastolic pressure in men, and in women the association was rather modest (Table 3).

Since both the prevalence of isolated systolic hypertension and abnormal pulse-wave recordings increase with age and are interrelated with each other, the risk of stroke was examined in multivariate analysis, including BP, pulse wave, and age

Table 2.—Mean Systolic Blood Pressure (mm Hg) by Vasculograph Class for Men Aged 45 to 74 Years

Class	Age Group, yr		
	45-54	55-64	65-74
1	134	138	138
2	135	139	144
3	137	146	149
4	135	143	150

(Table 4). Standardized logistic coefficients for the regression of stroke incidence on systolic pressure were substantial and highly significant ( $P < .01$ ) even taking age and pulse wave into account and excluding sub-

Table 3.—Risk of Stroke According to Systolic and Diastolic Blood Pressure

Population at Risk (Person-yr)	2-yr Rate per 1,000			Population at Risk (Person-yr)	2-yr Rate per 1,000			
	Men		Women		Men		Women	
	Crude	Age Adjusted	Crude	Age Adjusted	Crude	Age Adjusted	Crude	Age Adjusted
<b>Systolic pressure, mm Hg*</b>								
<140	6.73	5.0	6.3	7.02	5.5	5.8	6.3	
140-159	13.16	9.4	12.7	23.02	16.0	15.8	16.8	
>160	24.4	25.4	23.0	31.5	27.5	29.8	30.8	
<b>Diastolic pressure, mm Hg†</b>								
<90	5.4	5.4	2.0	7.26	7.0	8.6	8.6	
90-94	1.85	2.0	1.08	1.09	1.92	1.9	1.9	
≥95	3.7	4.0	2.4	3.82	3.7	3.6	3.6	

\*Subjects with diastolic pressure lower than 95 mm Hg for a 24-year follow-up for men and women aged 50 to 79 years.

†Subjects with systolic pressure exceeding 160 mm Hg for a 24-year follow-up for men and women aged 50 to 79 years.

Table 4.—Regression of Stroke Incidence on Age, Systolic Pressure, and Pulse-Wave Configuration\*

	Men		Women	
	Regression	t Value	Regression	t Value
Age	0.86	1.99	0.68	2.07
Systolic pressure	7.57	5.21	4.08	2.62
Pulse wave	0.87	1.43	1.03	1.55

\*Persons with diastolic pressure lower than 95 mm Hg, for men and women aged 50 to 79 years.

†For men, the number of stroke events was 44, and the number of subjects at risk was 668.

‡For women, the number of stroke events was 41, and the number of subjects at risk was 835.

tribute to risk taking age and vascular rigidity into account.

#### COMMENT

The data presented indicate that not only is isolated systolic hypertension a powerful contributor to stroke incidence, but that use of diastolic pressure in the elderly stroke candidate may not only be less efficient, but actually misleading. This could derive from the fact that diastolic pressure is less accurately determined by the indirect method in the elderly than is systolic pressure.

It is conceivable that isolated systolic hypertension in the elderly reflects rigid arteries and that it is this rather than the pressure that determines the risk of stroke. The analysis presented, using the depth of the dicrotic notch to reflect the elastic recoil of the arterial circulation, would seem to indicate that the pressure is not merely a sign of rigid vasculature but an independent contributor to risk (Table 4).

However, this conclusion depends on the credibility of the pulse-wave recording as an indicator of vascular rigidity. The mechanism by which the normal pulse wave is developed has been studied by physiologists over the past 35 years.<sup>11</sup> Pulse-wave recordings

have been compared in subjects with hypertension, arteriosclerosis, and diabetes.<sup>11,12</sup> Lax et al<sup>13</sup> concluded that the appearance of the dicrotic notch was the most important diagnostic feature of the peripheral pulse wave. Although the dicrotic notch has been attributed to rebound elastic recoil after aortic valve closure, peripheral factors including the tone of the smaller vessels and peripheral vascular resistance have been shown to influence the appearance of the dicrotic notch.<sup>14</sup> Induced peripheral vasoconstriction may cause the incisura to disappear.<sup>15</sup> However, in the absence of peripheral vasoconstriction, the persistence of a good dicrotic notch may well be a good measure of maintenance of normal elasticity. In the absence of cardiac failure or aortic valve disease, it seems reasonable to consider the incisura as largely a reflection of arterial elasticity and arteriolar muscular tone.

The loss of arterial elasticity with age presumably reflects either qualitative or quantitative changes in vascular elastin. However, not all reports have indicated a decline in elastin with age.<sup>11,14</sup> Elastin of older persons has been shown to contain more calcium.<sup>16</sup>

Studies at Framingham have shown a relationship of absence of the dicrotic notch to the prevalence of atherosclerotic cardiovascular disease.<sup>1</sup> Also, the loss of the dicrotic incisura increases with age so that by the ages of 65 to 74 years, less than 10% of persons have a normal pulse-wave tracing (Table 5). The prevalence of systolic hypertension and the pulse pressure increases with the degree of blunting of the dicrotic notch (Table 1). This increase in prev-

Table 5.—Prevalence of Peripheral Pulse-Wave Abnormality\*

Age Group, yr/No.	With Dicrotic Notch, %	
	Normal	Abnormal†
45-54/311	43.7	1.3
55-64/272	26.9	2.2
65-74/203	8.9	10.8

\*Vasculogram according to age, men aged 45 to 74 years.

†Absent dicrotic notch.

Table 6.—Prevalence of Hypertension\* by Vasculogram Class in Men Aged 45 to 74 Years

Class	Age Group, yr, %		
	45-54	55-64	65-74
1	12.5	20.6	16.7
2	14.1	7.1	25.0
3	15.3	32.5	28.0
4	25.0	33.3	36.4

\*Systolic pressure of greater than 160 mm Hg and diastolic pressure exceeding 95 mm Hg.

jects with diastolic pressures of 95 mm Hg or greater. The size of the coefficients for systolic pressure were even larger than those for age after standardizing for the different units of measurement. The coefficients for pulse wave were rather modest in comparison and not statistically significant. It thus appears that isolated elevations of systolic pressure con-

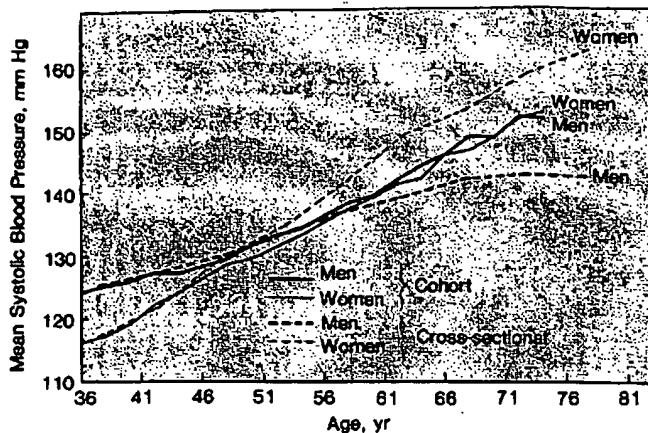


Fig 2.—Average age trends in systolic (left) and diastolic (right) blood pressure levels for cross-sectional and cohort data, examinations 3 to 10, Framingham study.

alence of isolated systolic hypertension with blunting of the dicrotic notch is more pronounced than noted for prevalence of ordinary hypertension (greater than 160 mm Hg systolic and 95 mm Hg diastolic on two successive determinations) (Table 6). All these findings are supportive of the contention that the dicrotic notch reflects arterial elasticity, albeit imperfectly.

Examination of age trends in BP in the Framingham cohort indicates that compared with diastolic, systolic pressures rise disproportionately with age consistent with a progressive loss of arterial elasticity (Fig 2). The prevalence of isolated systolic hypertension increases with age to a high level in the elderly and, using commonly accepted definitions ( $\geq 160$  mm Hg systolic and  $< 95$  mm Hg diastolic), affects 30% of elderly women and 18% of elderly men (Fig 3).

Although elevated pressures and systolic hypertension are definitely more prevalent in the elderly, there is no evidence that such pressure elevations are less dangerous than in the young with diastolic hypertension. Comparison of risk gradients for stroke based on systolic vs diastolic pressure shows nothing to indicate a closer relationship to the diastolic pressure component. (In a 20-year follow-up of men and women aged 45 to 74 years, the average standardized logistic coefficients for regression of stroke incidence was as follows: systolic BP and diastolic BP for men were .5966 and .5324, and for women, .6096 and .5924, respectively.)

Systolic hypertension appears to be

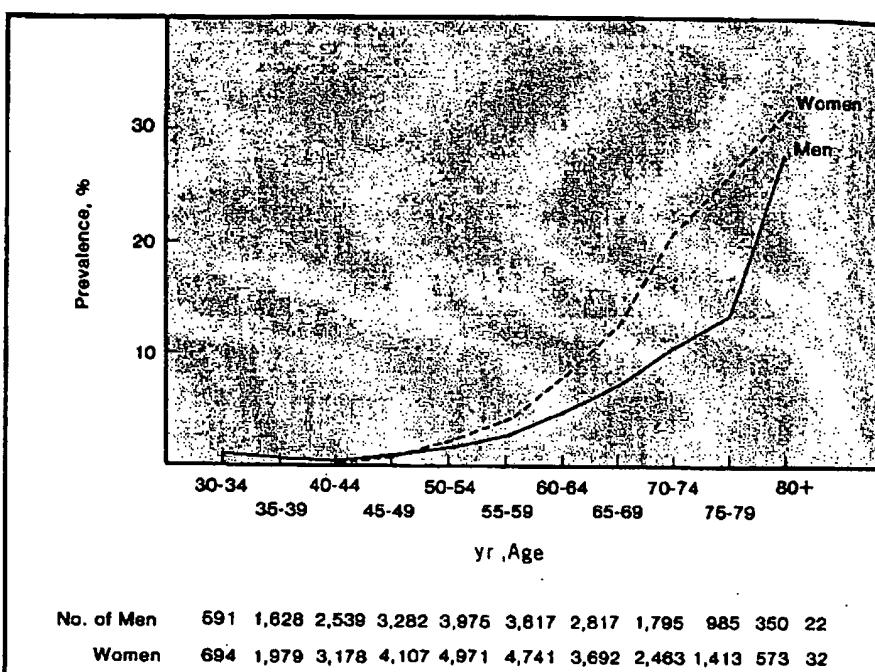


Fig 3.—Prevalence of isolated systolic hypertension by age and sex in 24-year follow-up in Framingham study.

a neglected precursor of stroke. Since systolic pressure increases more with age than diastolic, it is often regarded as a normal concomitant of aging.<sup>15-17</sup> The fact that hypertension in the elderly is predominantly systolic does not necessarily mean that it is an innocuous condition.<sup>18,19</sup> There is no reason why the damage caused by hypertension should derive more from the diastolic than the systolic component of the pressure.<sup>20</sup> One would expect subarachnoid or intracerebral hemorrhages to be provoked more by the peak pressure during the cardiac cycle than the pressure between beats.

There is still a question as to whether the demonstrated increased risk associated with systolic hypertension can be reduced by antihypertensive treatment and at what cost in inconvenience and side effects. Therapy for isolated systolic hypertension is successful less often than for diastolic hypertension, and it is sometimes necessary to reduce the diastolic pressure to extremely low values.<sup>21,22</sup>

The data presented indicate that the increased risk of stroke associated with systolic hypertension probably is a direct result of the pressure itself. This suggests that treatment to lower

the side effects of treatment would

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the systolic pressure may well be efficacious. A controlled trial to better determine the indications, contraindications, dosage, best drugs, side effects, benefits, and hazards would seem long overdue. Because of

the high risk of stroke in subjects with isolated systolic hypertension and the demonstration that it is the pressure per se that is responsible, this is a preventive challenge deserving attention.

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# JAMA

75 YEARS AGO

March 31, 1906

### The Neurons

Lewis F. Barker, M.D.

[Original Article, pp 929-930]

on as to increased ic hypertension at cost in s. Therapeutic than for t is some diastolic low val- cate that is associated robably is ure itself. t to lower

The neurohistologic world appears to be divided into two camps, that of the neuronists and that of the antineuronists. The controversy, curiously enough, has been a rather one-sided affair, though by no means wholly so. The so-called neuronists have spoken and written of the nervous system as a mass of nerve units or neurons and have devoted themselves chiefly to observations and experiments concerning the internal and external morphology of these units, their relations to one another, and especially their arrangements in chains and groups, and the relations of such chains and groups to function in health and in disease. With few exceptions they have refrained from controversy on the hypothetical side. The so-called antineuronists, ... while they have made some

admirable contributions to real knowledge, have devoted a remarkable amount of time and energy to polemical writing; one of them is the author of a book of nearly 500 pages in which few new facts, if any, are brought forward, the whole volume being given over to a condemnation of the neuron doctrine and a denunciatory arraignment of its supporters.

From controversial statements ... only one thing is clear, namely, that those who have made them are quarreling about matters of opinion more than about matters of fact. There is no reason why bitter dispute should long continue over easily verifiable fact. Experience teaches, however, that it is those opinions which are most feebly founded in fact and are least capable of proof that mankind is prone most passionately to defend. Science ought to try to avoid controversy by emphasizing facts and by properly estimating hypotheses. Further, scientific men should know that, once involved in discussion, nothing is gained by the bandying about of personalities; on the contrary, confidence is inspired by simple honesty in work, fairness to adversaries, moderation in statement and dignity in utterance. That was a homely but sensible saying of Truthful James when he declared that:

"I hold it is not decent for a scientific gent  
To say another is an ass—at least,  
to all intent;

Nor should the individual who happens  
to be meant  
Reply by heaving rocks at him, to any  
great extent."

By the use of ... two methods a newly recognized anatomic unit stood out, clearly visible in the tissues. To call it nerve cell was a little confusing, as that term had already been applied to the cell body in the gray matter independent of the related axis cylinder process. This unit included not only the old nerve cell with its dendrites, but also its axis cylinder process and all the collateral and terminal ramifications of the latter. Waldeyer suggested that it be called neuron, a name which speedily found its way in all languages, including our own. Waldeyer's article ... undoubtedly had great influence in quickly popularizing the neuron conception. A definite anatomic fact had been established, viz., the possibility of demonstrating in embryonic tissues by Golgi's method, and in adult tissues by Ehrlich's method, a hitherto nondemonstrable unit in anatomic structure. On the basis of embryologic and pathologic work which was brought into relation with this fact, a body of doctrines, often called the neuron doctrine, was built up. A sharp distinction between the *fact* and the associated *doctrine* should be borne in mind, for much of the subsequent dispute has been due to neglect in this regard.

## Multiple Risk Factor Intervention Trial

### Risk Factor Changes and Mortality Results

Multiple Risk Factor Intervention Trial Research Group

• The Multiple Risk Factor Intervention Trial was a randomized primary prevention trial to test the effect of a multifactor intervention program on mortality from coronary heart disease (CHD) in 12,866 high-risk men aged 35 to 57 years. Men were randomly assigned either to a special intervention (SI) program consisting of stepped-care treatment for hypertension, counseling for cigarette smoking, and dietary advice for lowering blood cholesterol levels, or to their usual sources of health care in the community (UC). Over an average follow-up period of seven years, risk factor levels declined in both groups, but to a greater degree for the SI men. Mortality from CHD was 17.9 deaths per 1,000 in the SI group and 19.3 per 1,000 in the UC group, a statistically nonsignificant difference of 7.1% (90% confidence Interval, -15% to 25%). Total mortality rates were 41.2 per 1,000 (SI) and 40.4 per 1,000 (UC). Three possible explanations for these findings are considered: (1) the overall intervention program, under these circumstances, does not affect CHD mortality; (2) the intervention used does affect CHD mortality, but the benefit was not observed in this trial of seven years' average duration, with lower-than-expected mortality and with considerable risk factor change in the UC group; and (3) measures to reduce cigarette smoking and to lower blood cholesterol levels may have reduced CHD mortality within subgroups of the SI cohort, with a possibly unfavorable response to antihypertensive drug therapy in certain but not all hypertensive subjects. This last possibility was considered most likely, needs further investigation, and lends support to some preventive measures while requiring reassessment of others.

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#### BACKGROUND

THE YEARS subsequent to World War II saw increasing evidence of the importance of arteriosclerosis and its complications as the leading cause of death in the United States. Scientific studies in the laboratory, clinic, and in population groups pointed to the contributing roles of diet, hypertension, cigarette smoking, diabetes, and

other risk factors in the genesis of coronary heart disease (CHD). Yet convincing demonstrations of the favorable effect of risk factor modification on CHD morbidity and mortality were not at hand by the 1960s.

For editorial comment  
see p 1501.

In July 1970, the National Heart and Lung Institute (NHLI) convened a Task Force on Arteriosclerosis specifically to develop a broad long-range plan for the study, control, and possible prevention of arteriosclerosis.<sup>1</sup> The Task Force concluded that the time had come for vigorous appli-

cation of existing knowledge for the purpose of determining whether CHD could be prevented. Among its final recommendations were (1) the advice not to institute a large-scale national diet-heart trial because of excessive cost and uncertain feasibility, and (2) a proposal that multiple risk factor intervention trials be undertaken to ascertain whether modification of elevated serum cholesterol levels, hypertension, and cigarette smoking in persons at increased risk of death from heart attacks would result in reduction of coronary death rates. With acceptance of the latter proposal, the NHLI prepared and distributed requests for participation of clinical and support centers in the Multiple Risk Factor Intervention Trial (MRFIT).

#### METHODS Organization

In 1972 and 1973, awards from the NHLI (later the National Heart, Lung, and Blood Institute, or NHLBI) were made to 22 clinical centers, a coordinating center, a laboratory center, a laboratory standardization center, and two electrocardiography centers. A policy advisory board, whose members had no formal association with any of the other participating units of the trial, was appointed by the Institute to provide advice on the overall course of the trial and to monitor the effects of intervention.<sup>2</sup> A steering committee comprised of investigators from the clinical and support centers and NHLBI staff was responsible for the scientific leadership of the trial.<sup>3</sup>

#### Design

The MRFIT design called for the recruitment of at least 12,000 men aged 35 to 57 years who were at increased risk of

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death from CHD, but had no clinical evidence of CHD. Persons were designated at "increased risk" if their levels of three risk factors—cigarette smoking, serum cholesterol, and blood pressure (BP)—were sufficiently high at a first screening visit to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study.<sup>1</sup> After about one third of the screening was completed and success in recruitment had been demonstrated, the 15% was changed to 10% to increase the average risk level of the eligible men. As an example of the application of this criterion, a man whose diastolic BP was 90 mm Hg and who reported smoking 30 cigarettes per day was risk-eligible at the 10% level if his serum cholesterol level was at least 295 mg/dL. The study was restricted to men because of their much higher risk of premature heart attack compared with women.

The men were to be randomized into two groups of approximately equal size. One group received a "special intervention" (SI) program aimed at cessation of cigarette smoking and reduction of elevated serum cholesterol and BP levels. Men in the other group, "usual care" (UC), were referred to their personal physicians or other community medical facility for such treatment of their risk factors as was considered individually appropriate.

#### Recruitment

As a first step in identifying at least 12,000 men eligible for the trial, 361,662 men were recruited for a first screening visit to determine CHD risk eligibility and to apply several exclusion criteria. Various recruitment techniques were used, with the most common procedure being to offer voluntary screening to industry or government employee groups. The number recruited for screening at each center ranged from 11,435 to 30,465. The men were informed at the first as well as at subsequent screening visits of the randomized nature of the trial.

#### Eligibility Criteria

Eligibility was determined at three successive screening visits (S<sub>1</sub>, S<sub>2</sub>, and S<sub>3</sub>). At S<sub>1</sub>, to determine risk for CHD, systolic and diastolic BPs were measured, the number of cigarettes smoked daily was ascertained, and a sample of blood was drawn for determination of the serum cholesterol level. Men were excluded from further screening on the basis of low risk, history of a heart attack, diabetes mellitus requiring medication, expected geographic mobility, a serum cholesterol level of 350 mg/dL or higher, or diastolic BP of 115 mm Hg or higher. The last two exclusions were made because of their special clinical features and therapeutic requirements. Of the men seen at S<sub>1</sub>, 25,545 (7.1%) qualified

and were invited to return for S<sub>2</sub>.

The second screening visit, S<sub>2</sub>, followed a 12-hour fast and included among other tests (1) a medical history and physical examination; (2) four BP determinations; (3) a locally read resting ECG; (4) a fasting blood sample for measurement of cholesterol, triglyceride, lipoprotein cholesterol, serum thiocyanate, and potassium levels, as well as a blood sample drawn one hour after a 75-g glucose load; (5) pulmonary function tests; (6) a posterior-anterior or chest film; (7) an assessment of willingness and ability to adhere to the proposed intervention program; and (8) a detailed explanation of the purposes of the trial and requirements for participation.

Reasons for excluding men at this visit included body weight greater than or equal to 150% of desirable weight; angina pectoris as determined by the Rose questionnaire<sup>2</sup>; history or ECG evidence of myocardial infarction; untreated symptomatic diabetes; diets incompatible with the MRFIT food pattern; treatment with guanethidine, hydralazine, insulin, oral hypoglycemic agents, or lipid-lowering agents; illnesses or disabilities likely to impair full participation in the trial; and diastolic BP of 120 mm Hg or higher. Of the 22,080 men seen at the S<sub>2</sub> visit, 15,791 men (71.5%) were invited to return for the third and final screening visit.

The third screening visit, S<sub>3</sub>, included (1) a resting and exercise ECG, (2) a detailed smoking questionnaire, and (3) a 24-hour dietary recall. A brief medical review and examination determined whether any major change in cardiovascular status had occurred since S<sub>2</sub>. The purpose and scope of the trial were again explained, and men who then signed the consent form were randomized by the coordinating center into either the SI or UC group. The randomization assignment was obtained by the local clinic coordinator who telephoned the coordinating center after eligibility and willingness to enter the trial had been established. Allocation to SI or UC was stratified by clinic and balanced in blocks of four or six, providing two groups of nearly equal size at each clinic, with 6,428 assigned studywide to SI and 6,438 to UC. Of the 14,111 men seen at S<sub>3</sub>, 12,866 were randomized into the trial, constituting a yield of 3.6% of men seen at S<sub>2</sub>. The first man was randomized in December 1973; the last randomization occurred on Feb 28, 1976.

#### Intervention Program

No intervention program was offered to the UC men who continued to be followed by their usual source of medical care, but they were invited to return once a year for a medical history, physical examination, and laboratory studies as listed herein. The results of the screening and annual examinations were provided to their per-

sonal physicians, who were informed as to the scientific objectives of the study.

The detailed components of the SI program have been reported earlier<sup>3,4</sup> and are summarized here. The initial phase of intervention was an intensive integrated effort to lower the three major risk factors. Immediately after randomization to the SI group, each cigarette smoker was counseled individually by a study physician in an effort to achieve cessation of smoking at that time. Shortly thereafter, each SI man was invited with his spouse or friend to a series of weekly group discussions addressing all three risk factors; uniformity of structure and content was sought by the use of common protocols and educational materials. Each group included about ten men and met for about ten sessions.

After the initial intensive intervention phase, individual counseling, planned and executed by an intervention team usually headed by a behavioral scientist and including nutritionists, nurses, physicians, and general health counselors, became the general approach in all three modalities. Participants in the SI group were seen every four months, and more often as needed for intervention purposes. The course of every SI participant was monitored to assess changes in risk factor status, the ultimate objective being to reach specific goals established for each individual.

**Hypertension.**—Hypertension was considered present if the man reported having antihypertensive medication prescribed for him by his personal physician (regardless of BP level), or if an untreated man was found to have a diastolic BP of at least 90 mm Hg on two consecutive monthly visits during the trial. The reading at the second of these visits was used to establish a goal BP of either a 10 mm Hg reduction or 89 mm Hg, whichever was lower; men who had a diastolic BP of 90 mm Hg or less who were already taking antihypertensive drugs prescribed by a personal physician were assigned a goal of 80 mm Hg. Before drug prescription, weight reduction was attempted for overweight men. Drugs were prescribed according to a stepped-care protocol beginning with the use of either hydrochlorothiazide or chlorothalidone. Reserpine, hydralazine, guanethidine, or certain alternate drugs were sequentially added if goal BP had not been achieved.<sup>5</sup> The protocol also included a provision for mild sodium restriction. Participants in the SI group who had been treated with BP medication by nonstudy physicians were usually transferred, with the permission of their private physicians, to the care of an MRFIT clinician.

**Nutrition.**—The nutrition intervention program sought to encourage the development of lifelong shopping, cooking, and eating patterns rather than to specify a

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structured diet.' Individual intervention goals for lowering serum cholesterol levels by an amount dependent on the entry level were established. Initially, eating patterns were recommended that reduced saturated fat intake to less than 10% of calories and dietary cholesterol intake to less than 300 mg/day, and increased polyunsaturated fat intake to 10% of calories. In 1976, the nutrition pattern was changed to specify that saturated fat be less than 8% of calories and dietary cholesterol less than 250 mg/day. Weight reduction was sought for men whose weight was 115% or greater of desirable weight by recommending reductions in caloric intake and increases in moderate forms of physical activity.

**Smoking.**—The smoking intervention program urged those SI participants who smoked cigarettes to quit; no systematic effort was made to alter the smoking habits of persons who smoked only pipes and cigars.<sup>9</sup> Dosage reduction, including switching to cigarettes low in tar and nicotine, was recommended only as an intermediate step to cessation. Conventional behavioral modification techniques were used throughout the trial; aversive techniques and hypnosis were used in selected instances during the final years. Particularly successful intervention approaches were the ten-week group sessions at the beginning of the trial and the five-day quit clinics during the final years.

#### Data Collection Methods

On or about each anniversary of randomization, participants in both the SI and UC groups returned for assessment of risk factor levels and morbidity status. Data collected at these annual visits, at screening, intervention, and four-month visits were sent to the coordinating center for processing and analysis. Serum cholesterol concentration obtained at S, the first screening visit, for risk eligibility purposes was determined at one of 14 local laboratories established for this purpose and monitored by the Centers for Disease Control (CDC) Lipid Standardization Laboratory and the coordinating center. All subsequent analyses of blood samples for levels of cholesterol, triglycerides, lipoproteins, creatinine, potassium, glucose, uric acid, SGOT, and thiocyanate were determined by the central laboratory using techniques previously described.<sup>10,11</sup>

Except for the ECG taken at S, and read locally for exclusion purposes, cassette tapes of all ECGs were sent to the ECG Center in Halifax, Nova Scotia, for computer processing and interpretation. A paper tracing produced from the cassette was then forwarded to the ECG Reading Center in Minneapolis for visual classification according to the Minnesota code. Major ECG abnormalities included major Q wave findings, ST segment elevations

and depressions, negative T waves, frequent ventricular premature beats (VPBs) ( $\geq 10\%$  of recorded beats), complete atrioventricular (AV) and bundle-branch block, and supraventricular tachycardia. Minor ECG abnormalities included high R waves, left axis deviation, and less frequent VPBs ( $<10\%$  of recorded beats). The treadmill exercise test at S, was done according to a modified Bruce protocol.<sup>12</sup>

Cigarette smoking was measured in two ways: (1) a participant interview for smoking behavior; and (2) thiocyanate-adjusted smoking and quit rates using serum thiocyanate level as an objective measure of smoking behavior.<sup>13</sup>

For analyses in this report, baseline BP is defined as the average of the two random-zero manometer readings at S, and S; BP at each follow-up visit is the average of the two random-zero readings at the visit. A participant was considered hypertensive at entry if his baseline diastolic BP was 90 mm Hg or higher or if he reported at S, having antihypertensive drugs prescribed for him. No attempt was made before randomization to alter antihypertensive medication for those already receiving such agents.

Serum cholesterol concentration was determined at S, and each annual follow-up visit using automated methods with periodic quality control developed by the CDC Lipid Standardization Laboratory.<sup>14</sup> Plasma cholesterol and triglyceride concentrations were obtained at S, and each annual visit except at 12 months. The cholesterol content of each lipoprotein fraction, estimated after heparin/manganese precipitation, was obtained at S, and at 24, 48, and 72 months.<sup>15</sup> All lipid determinations were performed on serum or plasma specimens collected after an overnight fast except for the serum cholesterol at the first screening visit.

Twenty-four hour dietary recalls were obtained at S, and at 12, 24, 36, 60 (SI men only), and 72-month visits through interview by an MRFIT nutritionist. Recalls were coded by a Nutrition Coding Center (NCC) with nutrient calculations made using version VI of the NCC food table.<sup>16</sup>

#### Sample Size and Statistical Power

In planning for the MRFIT, four key endpoints were identified: (1) death from CHD (the primary endpoint); (2) death from cardiovascular disease (CVD); (3) death from any cause; and (4) the combination of fatal CHD and nonfatal myocardial infarction. Data on the first three endpoints are presented in this report on mortality; morbidity data will be included in a subsequent report. Application of the logistic function with coefficients estimated from Framingham data to the observed risk factor combinations of the men randomized projected a six-year CHD death rate for UC men of 29.0 deaths per

thousand men. With a sample size of 12,866 (the number eventually randomized into the trial), a reduction in CHD mortality among SI men to 21.3 per thousand (26.6% reduction) could be detected with a probability of .88 using a one-sided test for a difference in proportions at a .05 level of significance. This reduction was determined by using the following anticipated intervention effects (and corresponding potential risk reductions): (1) a 10% reduction of serum cholesterol level if 220 mg/dL or higher—otherwise no change; (2) a 10% reduction of diastolic BP if 95 mm Hg or higher—otherwise no change; and (3) graded reductions in cigarette smoking as follows: 25% reduction for smokers of 40 or more cigarettes per day, 40% for smokers of 20 to 39 per day, and 55% for smokers of less than 20 per day. These anticipated differential intervention effects were based on experience in earlier smoking cessation programs.<sup>17</sup>

In addition, it was assumed that the corresponding groups of UC smokers at entry would have reductions during the course of the trial of 5%, 10%, and 15%, respectively, but that there would be no change in serum cholesterol or BP level in the UC group. Further allowances were incorporated for nonadherence by SI men (estimated to increase progressively to 50% by the end of six years), and for time to achieve maximum potential benefit of risk factor change (estimated to be a "lag" of three years). A similar calculation for the endpoint of death from any cause gave an estimate of power of .92. Statistical aspects of the design have been reported elsewhere.<sup>18</sup>

During the trial, subgroup hypotheses relative to mortality outcome were formulated by MRFIT investigators blinded to interim mortality data with the realization that power would be lower for their testing than for comparisons based on all SI and UC men. These hypotheses were based on the recognition that, in such a group of men at increased risk of coronary disease, a proportion would have advanced coronary atherosclerosis at entry even after excluding those with clinical evidence of CHD (history of myocardial infarction or angina, or ECG evidence of myocardial infarction). One of these hypotheses, that the intervention program would be especially effective in lowering CHD mortality for men with normal baseline resting ECGs, is referred to in this article.

#### Mortality Ascertainment

All participants were followed for a minimum of six years, with an average period of observation of seven years. Deaths were ascertained by clinic staff through contact with family or friends of the deceased, routine follow-up of missed clinic visits, response to postcards request-

Table 1.—Mean Values of Selected Variables at Entry for MRFIT SI and UC Men\*

	SI (n=6,428)	UC (n=6,438)
Screen 1		
Age, yr	46.2	46.1
Serum cholesterol, mg/dL	253.8	253.5
Diastolic BP, mm Hg	99.2	99.2
Cigarette smokers, %	63.8	63.6
Cigarettes smoked by smokers, No. per day	33.7	34.2
Black participants, %	7.2	7.2
Framingham 6-yr risk of CHD death, %	3.12	3.15
Screen 2		
Plasma cholesterol, mg/dL	240.3	240.6
Plasma LDL cholesterol, mg/dL	159.8	160.3
Plasma HDL cholesterol, mg/dL	42.0	42.1
Plasma triglycerides, mg/dL	194.7	193.9
Weight, lb	189.3	189.1
Serum thiocyanate, $\mu$ moles/L	191.0	191.1
Screen 3		
Minnesota codes 1.1-1.2.7 (definite myocardial infarction), %†	0.38	0.38
Minnesota codes 1.1-1.3 (definite or possible myocardial infarction), %	1.29	1.57
Major ECG abnormalities, %‡	4.4	4.6
Major or minor ECG abnormalities, %	28.4	27.5
Iachemic response to exercise, %§	12.5	11.9
Dietary data (24-hr recall)		
Energy, kcal	2,497	2,478
Saturated fatty acids, % of calories	14.0	14.0
Polyunsaturated fatty acids, % of calories	6.4	6.4
Alcohol, % of calories	7.3	7.6
Cholesterol, mg	454	448
Baseline		
Systolic BP, mm Hg	135.7	135.6
Diastolic BP, mm Hg	91.0	90.9
Hypertensive (baseline diastolic BP $\geq$ 90 mm Hg or on antihypertensive drugs at screen 2), %	82.6	82.0

\*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; CHD, coronary heart disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

†These men, who had been judged free of ECG evidence of myocardial infarction by clinic physicians in order to be eligible for randomization, were subsequently assigned these Minnesota codes by the ECG Center.

‡For detailed listing of Minnesota codes, see Table 7.

§Based on computer measurement of the ST depression integral.

ing change-of-address information sent twice yearly to UC participants, and searches of publicly accessible files of deceased persons.

To determine survival status as of Feb 28, 1982 (six years after the last day of randomization), a telephone or mail contact was attempted with each man not previously known to be deceased. The status of men not located by this procedure was sought using the files of the Social Security Administration and the service of a commercial firm specializing in methods of follow-up. The 15 SI and 15 UC men whose survival status remained unknown as of July 1, 1982, are included in the analyses as survivors to Feb 28, 1982.

Cause of death was assigned by a Mortality Review Committee, a three-member panel of cardiologists not associated with any MRFIT center and not privy to interim trial results. This committee, without knowledge of study group membership of the deceased, reviewed clinic records, hospital records, next-of-kin interviews, death certificates, and reports of

autopsies performed (31% of SI decedents, 33% of UC). Deaths ascribed to CHD were subclassified as (1) myocardial infarction (documented by clinical or autopsy evidence), with death occurring within 30 days of onset of symptoms or during hospitalization for acute myocardial infarction; (2) sudden death (within 24 hours of symptom onset and without documented myocardial infarction); (3) congestive heart failure due to CHD; or (4) death during hospitalization for surgery for CHD or from complications of such an operation.

#### Statistical Methods

Differences in baseline characteristics and in risk factor levels at annual follow-up visits between men randomly allocated to the SI and UC groups were tested for statistical significance using Student's *t* (two-sided) or the  $2 \times 2 \chi^2$  test without adjustment for multiple comparisons.

Risk factor changes over time are presented as mean values for all participants who attended each visit. (Results based on cohort analysis and data imputation pro-

cedures for missing values, such as substitution of either baseline or previous annual visit risk factor levels, did not differ from these in any substantial way.) Mortality results are presented as life-table functions using the Kaplan-Meier product limit method<sup>10</sup> and as the proportion of deaths as of Feb 28, 1982, among SI and UC participants. Significance testing of mortality results is limited to the key endpoints for the entire cohort. For the three key mortality endpoints, differences between all SI and UC participants are summarized using the log rank test.<sup>11</sup> For the primary endpoint of CHD death, a 90% confidence interval (CI) for the percentage difference,<sup>12</sup>  $[(UC-SI)/UC] \times 100$ , between all SI and all UC men in the proportion of deaths at the end of follow-up is given since the design of the trial was based on a one-sided test at the .05 probability level. For other comparisons, the more conventional 95% CI for the percentage difference is given.

The analysis of subgroups of men is, unless otherwise noted, restricted to groups defined by baseline characteristics. Men are classified, regardless of degree of adherence, as SI or UC based on the allocation at randomization.

## RESULTS

### Comparison of SI and UC Groups at Entry

The effectiveness of the randomization process in establishing two comparable groups at baseline is demonstrated by the excellent agreement in prerandomization levels of numerous risk factor and risk factor-related variables (Table 1). None of these differences is statistically significant at the .05 level.

### Follow-up Visit Record

The missed visit rates (the number of men alive at the time of the specified annual visit but who did not attend, divided by the number of men randomized) were 4.5% for SI and 5.2% for UC men at 12 months; these increased only slightly each year and, although somewhat higher for the UC group at each visit, remained below 10% through six years for both groups. Participants who were randomized early in the recruitment period came to the clinic for annual visits beyond the sixth; however, data on risk factor change is presented in this report only through the sixth, the last visit that the entire surviving cohort could have attended.

### Risk Factor Reduction

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the trial was to obtain adequate reductions, through intervention, of the three major modifiable CHD risk factors (Fig 1). For each of these, highly statistically significant ( $P < .01$ ) differences between the SI and UC groups were observed at each annual visit.

The mean diastolic BP at the first screening visit,  $S_1$ , for men subsequently randomized was 99.2 mm Hg. Baseline diastolic pressure, defined as the average of  $S_1$  and  $S_2$  random-zero readings, was 91.0 mm Hg, with regression to the mean probably accounting for much of the decrease from  $S_1$ . By 12 months, average reductions from baseline of 6.3 mm Hg for SI men and 2.5 mm Hg for UC men were observed (Table 2). By 72 months, these reductions were 10.5 mm Hg and 7.3 mm Hg, respectively. Of the men randomized, 19% reported at baseline being prescribed antihypertensive medication; at six years, 58% of SI men and 47% of UC men reported such prescription. Of SI men treated for hypertension, 88% had diastolic pressures lower than 90 mm Hg at six years. The average percent reduction from baseline to 72 months among all SI men with  $S_1$  diastolic pressure of 95 mm Hg or higher was 12%, a figure exceeding design expectations; however, the corresponding reduction for UC men (unanticipated in the design) was 8%. The SI-UC difference in diastolic BP averaged over annual visits was 4%, approximately 75% of the design goal used for sample size calculations. Among the 22 clinical centers, differences in mean diastolic BP at 72 months for SI and UC participants ranged from 0.2 to 5.1 mm Hg.

At the time of randomization, 59% of all men reported themselves as current cigarette smokers (Table 2). For men who reported smoking at  $S_1$ , stated quit rates at 12 months were 43% for SI men and 14% for UC men; at 72 months, these were 50% and 29%. Thiocyanate-adjusted quit rates at 12 months were 31% for SI men and 12% for UC; at 72 months, these were 46% and 29%, respectively. The reported and the thiocyanate-adjusted SI-UC differences, stated in terms of mean change in number of cigarettes smoked per day for all participants, exceeded design goals by 122% and 45%, respectively. At 72 months, the SI-UC differences in

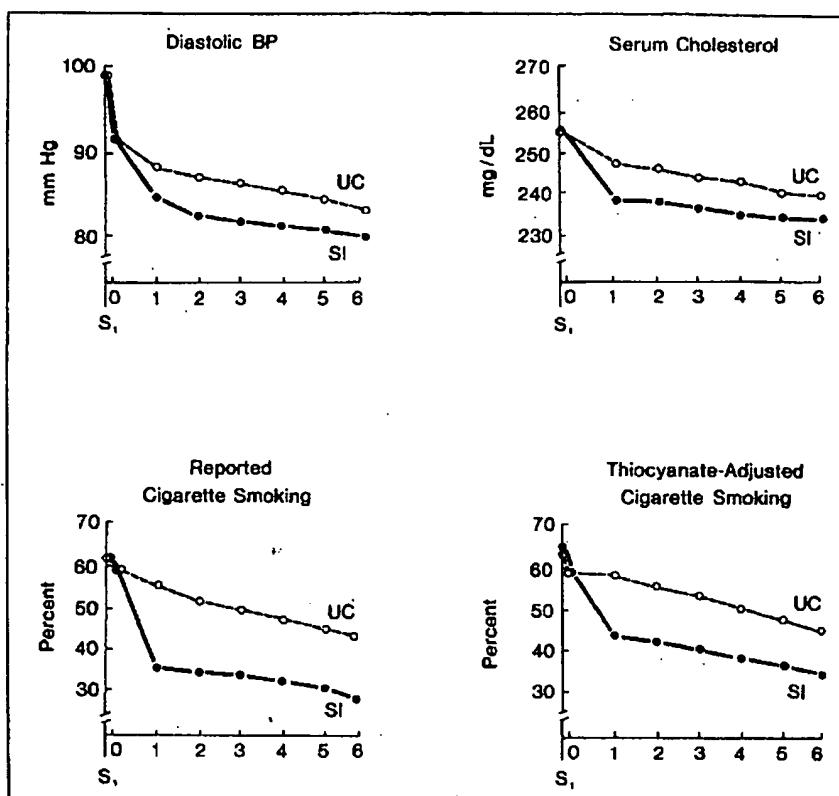


Fig 1.—Mean risk factor levels by year of follow-up for Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care;  $S_1$ , first screening visit.

Table 2.—Mean Risk Factor Levels at Screening and Annual Visits for MRFIT SI and UC Men\*

	Screening		Annual Visits, mo					
	$S_1$	$S_1/S_2$	12	24	36	48	60	72
SI	99.2	91.0‡	84.7	82.5	82.0	81.6	81.2	80.5
UC	99.2	90.9‡	85.4	88.9	88.3	86.8	84.6	83.6
Reported Cigarette Smoking, %								
SI	63.8	59.3	35.9	35.2	35.1	33.9	32.6	32.3
UC	63.5	59.0	65.6	62.2	60.6	48.2	46.7	46.6
Serum Cholesterol, mg/dL§								
SI	263.8	...	238.4	238.2	238.9	235.4	234.9	235.5
UC	263.5	...	246.8	246.0	244.2	243.4	240.6	240.3
Plasma Cholesterol, mg/dL§								
SI	...	240.3	229.8	228.1	227.2	226.6	228.2	
UC	...	240.6	237.2	236.1	234.7	232.9	233.1	
Plasma LDL Cholesterol, mg/dL								
SI	...	159.8	150.7	148.1	148.1	148.7	148.7	
UC	...	160.3	157.3	154.6	154.6	152.9	152.9	
Plasma HDL Cholesterol, mg/dL								
SI	...	42.0	42.8	42.8	42.8	41.7	41.7	
UC	...	42.1	43.3	43.0	43.0	41.9	41.9	
No. of Participants at Each Visit								
SI	6,428	6,428	6,112	6,895	6,883	5,791	5,682	6,754
UC	6,438	6,438	6,080	5,918	6,793	5,711	5,616	6,639

\*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

†All readings except  $S_1$  are by the random-zero manometer.

‡The average of  $S_1$  and  $S_2$  BP readings is defined as baseline and given here.

§Both serum and plasma cholesterol level determinations were made; the latter were consistently lower as reported by others.¶

Table 3.—Number of Deaths and Cumulative Mortality (per 1,000) by Year of Follow-up for MRFIT SI and UC Men\*

Year	No. of Deaths						Cumulative Mortality, Deaths per 1,000 Men					
	CHD		CVD		All Causes		CHD		CVD		All Causes	
	SI	UC	SI	UC	SI	UC	SI	UC	SI	UC	SI	UC
1	11	9	14	10	19	17	1.7	1.4	2.2	1.6	3.0	2.6
2	11	20	14	23	22	31	3.4	4.5	4.4	5.1	6.4	7.5
3	16	18	17	20	29	37	5.9	7.3	7.0	8.2	10.9	13.2
4	18	18	18	18	34	39	8.4	9.8	9.8	11.1	18.2	19.3
5	21	15	25	19	52	41	11.7	12.2	13.8	14.0	24.3	25.6
6	17	28	24	33	56	64	14.4	16.3	17.5	19.2	32.8	34.0
6-yr Total	92	104	112	123	211	219	...	...	...	...	...	...
As of												
2/28/82‡	115	124	138	145	265	280	17.9	19.3	21.5	22.6	41.2	40.4

\*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; CHD, coronary heart disease; CVD, cardiovascular disease.

†All men had at least six years of follow-up.

‡Mortality rates as of Feb 28, 1982, the last day of follow-up for all men, are simple proportions; for years 1 through 6, life table rates are given.

Table 4.—Frequency Distribution of Deaths by Cause for MRFIT SI and UC Men\*

Cause of Death	Special Intervention		Usual Care	
	n	% of Total	n	% of Total
Coronary heart disease (CHD)	115	43.4	124	47.7
Myocardial infarction (MI)†	38	14.3	35	13.5
Sudden death (without documented MI)				
Within 60 min of being seen alive	54	20.4	58	21.6
Within 24 hr, but more than 60 min of being seen alive	18	6.6	25	9.6
Congestive heart failure due to CHD‡	1	0.4	4	1.6
Coronary surgery deaths	4	1.6	4	1.5
Other cardiovascular disease	23	8.7	21	8.1
Stroke	13	4.9	11	4.2
Hypertension with left ventricular failure	0	0.0	1	0.4
Pulmonary embolus	3	1.1	3	1.2
Other	7	2.6	6	2.3
Noncardiovascular disease	116	43.6	109	41.9
Neoplasia	81	30.8	69	26.5
Lung	34	—	28	—
Colorectal	8	—	6	—
Other GI	20	—	11	—
Other	18	—	24	—
Liver disease	4	1.6	4	1.6
Lung disease	2	0.8	2	0.8
Suicide	7	2.8	6	3.1
Homicide	5	1.9	5	1.9
Accident	10	3.8	14	5.4
Other	7	2.8	7	2.7
Unknown cause of death	11	4.2	6	2.3
Total	265	100.0	280	100.0

\*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; GI, gastrointestinal tract.

†Myocardial infarction, documented by clinical or autopsy evidence, with death occurring within 30 days of onset of symptoms or during hospitalization for acute MI.

‡Without documented MI.

§Death from hospitalization for surgery for coronary heart disease or from complications of such an operation.

thiocyanate-adjusted quit rates for the 22 centers ranged from 5% to 24%.

Mean plasma cholesterol level at S, (relatively free of regression to the

mean because, unlike the cholesterol level at S, it was not used as an eligibility criterion to select men at high risk) was 240 mg/dL. After two years there were reductions of 10.4

mg/dL for SI men and 3.4 mg/dL for UC men; after six years the mean levels were 12.1 mg/dL and 7.5 mg/dL below baseline for SI and UC men, respectively. These reductions, which primarily represent changes in low-density lipoprotein (LDL)-cholesterol and not high-density lipoprotein (HDL)-cholesterol (Table 2), amount to an SI-UC difference in total cholesterol of 4.6 mg/dL, or 2%. With the less-than-anticipated reduction among SI men and the unexpected decline among UC men, the SI-UC difference was about 50% of goal. Differences among the 22 centers in mean plasma cholesterol levels varied from -1.6 to 10.4 mg/dL at 72 months.

Several approaches were used to estimate the combined risk factor reductions. Incorporating the observed changes for the three risk factors into an expression for the relative odds (SI/UC) of CHD death using a Framingham risk function yielded an estimated relative odds 30% short of goal at 12 months, 10% short at 48 months, and nominally at goal at 72 months. This convergence to design goal largely reflects the design prediction of larger initial differentials followed by increasingly poor adherence, whereas the data show long-term maintenance of more modest initial differences. An analysis based on averaging calculated CHD risks for each participant over the six years of follow-up, indicated a potential net CHD mortality lowering of 22.2% rather than the 26.6% considered possible at the design stage; thus, this computation implies achievement of 83% of the SI-UC risk factor difference initially assumed in the design.

#### Mortality, All SI and UC Participants

As of Feb 28, 1982, after an average period of follow-up of seven years, there were 260 deaths among UC men, of which 124 were ascribed to CHD and 145 to cardiovascular causes (including CHD). Of 265 SI deaths, 115 were ascribed to CHD and 138 to CVD (Tables 3 and 4). The key mortality endpoints of CHD and CVD were 7.1% and 4.7% less, respectively, in the SI compared with the UC group, while the death rate for all causes was 2.1% higher for the SI men. The corresponding life table (log rank) Z values for the endpoints are

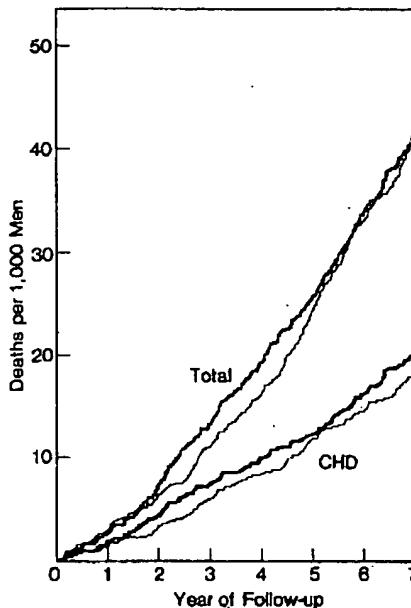


Fig 2.—Cumulative coronary heart disease (CHD) and total mortality rates for Multiple Risk Factor Intervention Trial Research Group participants. Heavy line indicates men receiving usual care (UC); thin line, men receiving special intervention (SI). Number of men alive with follow-up of seven years or longer: 3,117 UC and 3,118 SI.

+0.6, +0.4, and -0.2. None of these is statistically significant. A slight mortality advantage of the SI group, as shown by the separation of the cumulative mortality curves beginning at about two years, waned by year 5 (Fig 2). Of the 22 clinical centers, 11 had more CHD deaths among UC men than among SI; for total mortality, ten centers had more UC than SI deaths.

The number of deaths from noncardiovascular causes was also similar in the two groups (116 SI v 109 UC). There were 81 cancer deaths in the SI group and 69 in the UC, resulting from lung cancer (34 SI v 28 UC), colorectal cancer (8 SI v 6 UC), other gastrointestinal neoplasms (20 SI v 11 UC), and other neoplasia (19 SI v 24 UC).

The number of deaths in the UC group was substantially short of expectation for the six complete years of follow-up as well as for the average follow-up period of seven years. Based on design risk factor change assumptions and Framingham risk functions, 442 deaths (including 187 from CHD) were expected by the end of six years of follow-up among the 6,438 UC men; only 219 (including 104 from CHD)

Table 5.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Baseline Risk Factor Levels\*

	No. of Participants		CHD Deaths		Total Deaths	
	SI	UC	SI	UC	SI	UC
<b>Nonhypertensive†</b>						
Nonsmokers at S <sub>1</sub>						
Serum cholesterol						
<250 mg/dL	102	128	1(9.8)	1(7.8)	3(29.4)	2(16.6)
≥250 mg/dL	415	432	3(7.2)	4(9.3)	5(12.0)	6(13.8)
Smokers at S <sub>1</sub>						
Serum cholesterol						
<250 mg/dL	848	844	16(18.9)	11(13.0)	38(42.6)	30(35.5)
≥250 mg/dL	1,048	1,041	15(14.3)	29(27.9)	47(44.9)	63(50.9)
<b>Hypertensive‡</b>						
Nonsmokers at S <sub>1</sub>						
Serum cholesterol						
<250 mg/dL	820	627	2(3.2)	11(17.5)	14(22.6)	25(39.8)
≥250 mg/dL	1,188	1,180	23(19.4)	19(16.4)	42(35.4)	37(31.9)
Smokers at S <sub>1</sub>						
Serum cholesterol						
<250 mg/dL	1,388	1,369	30(21.8)	28(20.5)	68(49.0)	68(48.2)
≥250 mg/dL	823	837	25(30.4)	21(25.1)	50(60.8)	41(49.0)
<b>Subtotals</b>						
Nonhypertensive	2,409	2,445	35(14.5)	45(18.4)	91(37.8)	81(37.2)
Hypertensive	4,019	3,993	80(19.9)	79(19.8)	174(43.3)	169(42.3)
<b>Serum cholesterol</b>						
<250 mg/dL	2,956	2,968	49(16.8)	51(17.2)	121(40.9)	123(41.4)
≥250 mg/dL	3,472	3,470	68(19.0)	73(21.0)	144(41.5)	137(39.6)
<b>Nonsmokers at S<sub>1</sub></b>						
Nonhypertensive	2,325	2,347	29(12.5)	35(14.9)	64(27.6)	70(29.8)
Hypertensive	4,103	4,091	88(21.0)	89(21.8)	201(49.0)	190(46.4)
<b>Total</b>						
	6,428	6,438	115(17.9)	124(19.3)	265(41.2)	260(40.4)

\*For Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; CHD, coronary heart disease.

†Baseline diastolic BP (average of two R-Z readings at S<sub>1</sub> and S<sub>2</sub>) less than 90 mm Hg and not receiving antihypertensive treatment at S<sub>1</sub>.

‡Baseline diastolic BP ≥ 90 mm Hg or receiving antihypertensive treatment at S<sub>1</sub>.

Table 6.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Hypertensive Status at Baseline\*

	No. of Participants		CHD Deaths		Total Deaths	
	SI	UC	SI	UC	SI	UC
<b>Nonhypertensive†</b>						
Nonhypertensive	2,409	2,445	35(14.5)	45(18.4)	91(37.8)	81(37.2)
<b>Hypertensive‡</b>						
Hypertensive	4,019	3,993	80(19.9)	79(19.8)	174(43.3)	169(42.3)
Receiving treatment at S <sub>1</sub>						
Receiving treatment at S <sub>1</sub>	1,261	1,227	28(22.2)	26(21.2)	59(46.8)	54(44.0)
Not receiving treatment at S <sub>1</sub> , mm Hg						
90-945	1,157	1,181	17(14.7)	12(10.2)	47(40.6)	31(28.2)
95-995	830	846	19(22.9)	19(22.5)	43(51.8)	39(48.1)
≥1005	771	739	16(20.8)	22(29.8)	25(32.4)	45(50.9)
<b>Total</b>						
	6,428	6,438	115(17.9)	124(19.3)	265(41.2)	260(40.4)

\*For Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; CHD, coronary heart disease.

†Baseline diastolic BP (average of two R-Z readings at S<sub>1</sub> and S<sub>2</sub>) less than 90 mm Hg and not receiving antihypertensive treatment at S<sub>1</sub>.

‡Baseline diastolic BP ≥ 90 mm Hg or receiving antihypertensive treatment at S<sub>1</sub>.

§Baseline diastolic BP.

occurred. By the end of follow-up for all men, the total of 260 UC deaths (including 124 from CHD) was still well below the number expected for the six-year follow-up period. The approximate 90% CI for the percentage change in CHD mortality attributable to MRFIT intervention is therefore large, ranging from a 25%

decrease to a 15% increase.

#### Mortality In Baseline-Defined Subgroups

Comparisons of mortality rates for SI and UC men within subgroups defined by prerandomization characteristics preserve the comparability provided by the randomization but

Table 7.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Hypertensive Status at Baseline and by Presence of Resting ECG Abnormalities\*

	No. of Participants	CHD Deaths		Total Deaths		
		SI	UC	SI	UC	
<b>Nonhypertensive</b>						
Resting ECG abnormalities†						
Absent	1,817	1,862	24(13.2)	30(16.1)	71(39.1)	63(33.8)
Present	592	689	11(18.6)	16(25.7)	20(33.8)	28(48.0)
Total	2,409	2,445	35(14.5)	45(18.4)	91(37.8)	91(37.2)
<b>Hypertensive</b>						
Resting ECG abnormalities†						
Absent	2,786	2,808	44(15.8)	58(20.7)	100(35.8)	122(43.4)
Present	1,233	1,185	36(29.2)	21(17.7)	74(60.0)	47(38.7)
Total	4,018	3,993	80(19.9)	79(19.8)	174(43.3)	169(42.3)

\*For Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; MC, Minnesota Code.

†Abnormalities include high R waves in the precordial leads (MC, 3.1, 3.3, 3.4; N=1,410), negative T waves (MC, 5.1-5.3; N=511); R-R' pattern (MC, 7.5; N=488); ectopic ventricular premature beats (MC, 8.1; N=452); left axis deviation  $\leq -30^\circ$  (N=380); incomplete RBBB (MC, 7.3; N=359); ST depression (MC, 4.1-4.3; N=237); ST elevation (MC, 9.2; N=240); major Q waves (MC, 1.1-1.3; N=184); short P-R (MC, 6.5; N=109); first degree atrioventricular block (MC, 6.3; N=88); supraventricular tachycardia (MC, 8.4; N=38); right axis deviation  $\geq +120^\circ$  (N=17); and other rare conditions (N=36).\*

Table 8.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Baseline Risk Factor Levels for the Subgroup of MRFIT SI and UC Participants Without Resting ECG Abnormalities at Entry\*

	No. of Participants	CHD Deaths		Total Deaths		
		SI	UC	SI	UC	
<b>Nonhypertensive</b>						
Nonsmokers at S,						
Serum cholesterol						
<250 mg/dL	78	83	1(12.8)	1(10.8)	3(38.5)	2(21.5)
$\geq 250$ mg/dL	324	340	1(3.1)	3(8.8)	3(9.3)	3(8.8)
Smokers at S,						
Serum cholesterol						
<250 mg/dL	616	635	11(17.9)	8(12.6)	28(45.6)	21(33.1)
$\geq 250$ mg/dL	799	794	11(13.8)	16(22.7)	37(48.3)	37(48.6)
<b>Hypertensive</b>						
Nonsmokers at S,						
Serum cholesterol						
<250 mg/dL	439	445	1(2.3)	7(15.7)	9(20.5)	17(38.2)
$\geq 250$ mg/dL	861	852	13(15.3)	15(17.8)	23(27.0)	27(31.7)
Smokers at S,						
Serum cholesterol						
<250 mg/dL	928	922	21(22.6)	21(22.8)	45(48.5)	49(53.1)
$\geq 250$ mg/dL	567	589	9(15.9)	15(25.5)	23(40.6)	29(49.2)
<b>Subtotals</b>						
Nonhypertensive	1,817	1,862	24(13.2)	30(16.1)	71(39.1)	63(33.8)
Hypertensive	2,786	2,808	44(15.8)	58(20.7)	100(35.8)	122(43.4)
Serum cholesterol						
<250 mg/dL	2,081	2,095	34(16.5)	37(17.7)	85(41.2)	89(42.5)
$\geq 250$ mg/dL	2,541	2,575	34(13.4)	51(19.8)	88(33.8)	96(37.3)
Nonsmokers at S,	1,692	1,730	18(9.5)	26(15.0)	38(22.6)	49(28.3)
Smokers at S,	2,910	2,940	52(17.9)	62(21.1)	133(45.7)	136(48.3)
Total	4,602	4,670	68(14.8)	88(18.8)	171(37.2)	185(39.6)

\*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; CHD, coronary heart disease.

†Baseline diastolic BP (average of two R-Z readings at S<sub>1</sub> and S<sub>2</sub>) less than 90 mm Hg and not receiving antihypertensive treatment at S<sub>1</sub>.

‡Baseline diastolic BP  $\geq 90$  mm Hg or receiving antihypertensive treatment at S<sub>1</sub>.

have less precision as a result of the reduced sizes of the groups. There is also the increased likelihood of over-interpreting nominally significant differences resulting from the examination of multiple comparisons, some

of which were defined post hoc. However, the subgroup findings need exploration, especially to provide insight into the overall result and to indicate areas for further investigation.

The relationship of mortality to baseline levels of the three risk factors is shown in Table 5, where numbers of deaths by cause together with corresponding mortality rates are given for SI and UC men. The mortality rates for smokers, for hypercholesterolemia ( $\geq 250$  mg/dL) and for hypertensive men are given as subtotals in the lower rows. For each of these three groups, the mortality rates are similar for SI and UC men. However, it must be remembered that subgroups defined by the presence or absence of one of the three major risk factors are not otherwise comparable; for example, because of the selection procedure used, nonsmokers have on the average higher blood cholesterol and BP levels than smokers. Despite this complexity, it may be noted in the subtotals that CHD mortality, and in most cases total mortality, tends to be higher in smokers, in participants with hypercholesterolemia, and in those with hypertension, supporting the risk factor status of these variables within this cohort.

Among the group of all nonhypertensive men at baseline, there was a 21% lower CHD death rate (CI, -22% to 50%) for the SI group compared with UC men, but no comparable difference in deaths from all causes. Of the four substrata of men not hypertensive at baseline, the largest, consisting of cigarette smokers who were hypercholesterolemic, is of particular interest for its resemblance to the group of men in the Oslo primary prevention trial that recently reported positive findings (see Comment). The CHD mortality rate is 49% lower (CI, 8% to 75%) for the SI group compared with the UC group (15 SI deaths v 29 UC deaths), with a smaller difference observed for total mortality. Given the presence of both cigarette smoking and hypercholesterolemia, BP levels of men in this substratum of those not hypertensive at baseline were lower than those for the other three substrata, as a result of the risk-selection criteria; consequently, a relatively small percentage of the SI men in this substratum subsequently became hypertensive and received antihypertensive treatment.

Of the four substrata of hypertensive men, only in the smallest, consisting of nonsmokers who were not

hypercholesterolemic, was the CHD rate lower for SI men. With only one of the three risk factors present, this group, to meet the MRFIT risk-eligibility criteria, was necessarily made up of men with more severe degrees of hypertension.

A more detailed breakdown by hypertensive status at entry is given in Table 6. Among hypertensive men not receiving treatment at entry, the differences in SI and UC CHD and total mortality rates differ by level of baseline diastolic BP. The percentage differences in CHD mortality rates are -45% (17 SI CHD deaths  $\nu$  12 UC), -2% (19 SI CHD deaths  $\nu$  19 UC), and +30% (16 SI CHD deaths  $\nu$  22 UC), respectively, for participants with baseline diastolic BP levels of 90 to 94, 95 to 99, and 100 mm Hg or higher. The corresponding differences for total mortality are -55% (47 SI deaths  $\nu$  31 UC), -12% (43 SI deaths  $\nu$  39 UC), and +47% (25 SI deaths  $\nu$  45 UC).

Analyses related to one of the formal subgroup hypotheses (see Methods) suggested a possible explanation for the results observed in hypertensive men. Abnormalities on the baseline resting ECG seemed to be associated with an excess of CHD mortality in the SI compared with the UC group, with the effect limited to hypertensive persons (Table 7). For the group of hypertensive men without ECG abnormalities, a 24% lower death rate was noted in the SI group (44 SI CHD deaths  $\nu$  58 UC). This difference is similar to the 21% found for normotensive men with or without ECG abnormalities (35 SI CHD deaths  $\nu$  45 UC). For the group of hypertensive men with ECG abnormalities, there were 15 more SI deaths than UC (36 SI CHD deaths  $\nu$  21 UC). This percentage difference (-65%) is larger than, and in the opposite direction from, the corresponding difference for hypertensive men without ECG abnormalities. Similar findings, though not as pronounced, are found for total mortality (Table 7).

With this possibility that participants with abnormal ECG at baseline responded adversely to MRFIT intervention, the mortality results are retabulated by baseline risk factors for the 72% of men with a normal baseline resting ECG (Table 8). Such analyses are complicated because of

Table 9.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) for Smokers at Entry S, by Smoking Status at 12 Months and Amount Smoked at Entry\*

	No. of Participants	CHD Deaths		Total Deaths	
		Did Not Quit†	Quit†	Did Not Quit†	Quit†
<b>Special Intervention</b>					
1-29 cigarettes/day					
Reported at S,	454	806	6(13.2)	19(23.6)	13(28.6)
≥30 cigarettes/day					
Reported at S,	537	12,036	5(9.3)	39(19.2)	18(29.8)
<b>Usual care</b>					
1-29 cigarettes/day					
Reported at S,	159	1,021	3(18.9)	23(22.5)	8(50.3)
≥30 cigarettes/day					
Reported at S,	215	2,435	1(4.7)	47(19.3)	7(32.6)
					101(41.5)

\*For Multiple Risk Factor Intervention Trial Research Group participants. CHD indicates coronary heart disease. Deaths during the first year of follow-up are excluded.

†Quitters are S, smokers who reported quitting at 12 months with serum thiocyanate levels (at 12 months) lower than 100  $\mu$  mole/L.

the previously mentioned reciprocal and overlapping relationships of risk factor levels among the participants. For each subgroup listed in the lower half of Table 8, the SI men experienced fewer CHD deaths than did the corresponding UC group. A comparison of the results in Table 8 for men without ECG abnormalities at baseline with those for the total cohort in Table 5 reveals that for nearly all risk factor combinations there were fewer SI CHD deaths than UC for this large subgroup. There is a difference in CHD mortality of 24% (CI, -13% to 49%) for hypertensives without ECG abnormalities, and a 32% difference (CI, -3% to 57%) for those with cholesterol levels of 250 mg/dL or higher and without ECG abnormalities. The lower CHD mortality for SI compared with UC men in these subgroups, consisting of a large majority of the total MRFIT cohort, is similar to the mortality reduction expected based on the design of the trial.

#### Mortality in Subgroups Defined After Randomization

Since the smoking intervention was the most successful relative to the risk factor design goals, yet the CHD mortality differences between SI and UC men who had been smokers at baseline were modest (Tables 5 and 8), the relationship between smoking cessation and mortality was examined further. In men who quit smoking during the first year, subsequent death rates were compared with the rates in those who continued to smoke, controlling for the reported number of cigarettes per day at baseline (Table 9). It must be emphasized

that this kind of analysis does not preserve the randomized controlled design of the MRFIT, and must be interpreted with regard for the possibility of confounding by many factors. In both the SI and the UC groups, those who quit smoking had significantly lower rates of CHD and, for the most part, total mortality. Multivariate analyses controlling for critical variables, including the other major risk factors, have consistently supported the relationship between smoking cessation and CHD mortality.

#### COMMENT Strengths and Limitations of the Data

This large and complex trial was operationally successful. The recruitment phase was completed in a 28-month period and, in numbers recruited, exceeded the design goal. Randomization proceeded without incident, the two randomized groups being well balanced on numerous relevant characteristics. The completeness of follow-up exceeded expectations, with 91% of those alive returning for the sixth annual visit. For mortality endpoints, requirements of thorough documentation of all deaths and "blinded" classification of causes of death were met.

Intervention accomplishments in the SI group, which have been reported in detail,<sup>19</sup> were substantial: smoking cessation was much more successful than had been expected, the BP reduction in the SI group exceeded the desired drop in diastolic BP, and the effect on cholesterol lowering was considerable but less

than had been sought. A notable achievement of the intervention program was a continued decline in mean risk factor levels after the substantial drop in the first year.

Risk factor changes were also observed in the UC group, though to a lesser degree. Whereas it had been projected on the basis of the best information available ten years ago that this group would exhibit over six years no important changes in BP and serum cholesterol levels, and only minimal change in smoking habits, the actual findings were very different. Sizable reductions occurred in the levels of all three risk factors for UC men. Thus, over six years, reported cigarette smoking declined from 59% to 46%, the diastolic BP from a baseline value of 90.9 to 83.6 mm Hg, and plasma cholesterol levels from 241 to 233 mg/dL. Also, 47% of the UC men were receiving antihypertensive medication at the end of the sixth year compared with 19% at baseline.

The cause of these unanticipated changes in the UC group is speculative. Contributing elements to the risk factor reductions may include the psychological impact on the UC men of enrollment in a trial limited to persons at high risk of heart attacks, the possibility that persons volunteering for a six-year trial are unusually health conscious and motivated to change, sensitization of the UC men to their risk factor status resulting from annual visits to the clinical centers, and the broad influence of health education in the United States aimed at modifying all of the three risk factors. The physicians of the UC men may well have instituted their own preventive programs. Ethical considerations prompted notification of these physicians of the findings from each annual visit, although the MRFIT centers made no recommendation regarding intervention for UC men.

The risk factor changes in the UC group may be relevant to one of the assumptions on which the power of the trial was based and that has been shown to be inaccurate. The number of deaths in the UC group was substantially short of expectation. By the end of follow-up (an average of 7.0 years) for all men, the total of 260 UC deaths (including 124 from CHD) was still slightly less than two thirds the

number expected for the six-year follow-up period.

Several factors may have contributed to the lower-than-expected UC mortality: (1) the recent reduction in CHD mortality in the United States, the reasons for which are still not totally understood<sup>19</sup>; (2) exclusion criteria applied to the MRFIT screened group that may have been more stringent than those applied to data from the Framingham cohort during the design phase of MRFIT, resulting in the selection of men with a lower than expected mortality in both the SI and UC groups; (3) the phenomenon of lower-than-expected mortality in almost all clinical trials involving human volunteers; and (4) finally, the substantial risk factor changes made by UC men, as mentioned previously. The latter possibility can be entertained only if one assumes that risk-factor modification is effective in reducing mortality in high-risk men aged 35 to 57 years, the question the trial was designed to test.

The lower-than-predicted mortality for the UC group has the important effect of lowering the power from .88 to .75 for detecting the 26.6% SI-UC difference in mortality specified in the design. Furthermore, if the risk model based on Framingham data were accurate in predicting potential risk reduction, the unexpected decreases in UC risk-factor levels would also affect the power unfavorably. The power, based on the observed UC mortality rate, for detecting the 22% difference in CHD mortality predicted by the risk factor difference actually achieved, is about 0.6.

#### Interpretation of Mortality Results

The finding of percentage differences of only +7%, +5%, and -2% for CHD, CVD, and all-cause mortality rates, respectively, deserves careful examination. At least three possible explanations for these results must be considered: (1) such an intervention program is without benefit in terms of substantial decreases in mortality; (2) the intervention program does affect CHD mortality, but the benefit was not observed in this study; or (3) one or more constituents in the intervention program may have had an unfavorable effect on survival in some subgroups offsetting beneficial effects of others.

The first possibility, of ineffective-

ness on CHD, CVD, and total mortality of programs to reduce cigarette smoking, treat hypertension with drugs, and lower elevated serum cholesterol levels by diet, seems inconsistent with most published scientific data: clinical, pathological, animal experimental, and epidemiologic.<sup>20</sup> The trial was of course initiated to test this question in high-risk middle-aged men. Only one controlled trial limited solely to testing the benefit of reduction in or cessation of cigarette smoking has been executed; its results were inconclusive, but showed a favorable trend for CHD mortality.<sup>21</sup> A large body of scientific data supports the conclusion that cigarette smokers who reduce the amount of smoking or give it up entirely have improved life expectancy.<sup>22</sup> It is not clear, however, how long it takes after modification of smoking—especially heavy smoking—for favorable alterations of mortality rates to occur, and it may take longer than the seven-year duration of this trial to be clearly demonstrated.<sup>23</sup> Somewhat contrary to the possibility of a delayed effect is the observation that CHD mortality within the SI group subsequent to the first year of follow-up diverges sharply depending on smoking status at the 12-month visit. The rate in quitters who had smoked at least 30 cigarettes per day is approximately half that of those who continue smoking. Such within-group analyses, however, do not make use of the randomized control design of a clinical trial, and the results, while suggestive, leave open the possibility of confounding by other factors.

Regarding hypertension, a beneficial impact of drug treatment by a "stepped-care" protocol, as contrasted with "referred care," on total mortality has been described in a population of 10,940 men and women by the Hypertension Detection and Follow-up Program (HDFP).<sup>24</sup> For persons in the age group 30 to 49 years at entry, the difference in total mortality was 5.7%; for persons aged 50 to 59 years it was 25.3%.<sup>24</sup> The Australian National Blood Pressure Study, a placebo-controlled primary prevention trial in 3,427 men and women with mild hypertension, reported significantly fewer morbid and fatal events, including significantly fewer deaths from cardiovascular disease, in persons aged 30 to 69 years

who were treated with antihypertensive medication, but the corresponding percentage difference for all endpoints in the subgroup of men aged 30 to 49 years, though similar in magnitude, lacked statistical significance.<sup>23</sup> The earlier classic report from the Veterans Administration Cooperative Study concluded that treatment was effective in preventing congestive heart failure and stroke, but no statistically significant benefit for CHD mortality (six in the treated group, 11 in the placebo group) was found.<sup>24</sup>

In the area of lipid-lowering diet, some controversy has existed for years as to precise benefits, although most scientific including public health groups have concluded that benefits do indeed exist.<sup>11-13</sup> For example, the Los Angeles Veterans Administration Study, in a population of 846 institutionalized men aged 55 years and older, demonstrated significant reduction in mortality from atherosclerotic diseases, but not in total mortality.<sup>10</sup> The recently concluded Oslo trial in 1,232 high-risk nonhypertensive men aged 40 to 49 years combining lipid-lowering dietary intervention with smoking cessation showed statistically significant reductions in sudden coronary death and in CHD incidence, and substantial, though nonsignificant, reductions in CHD and total mortality. In the Oslo study, differential quit rates for cigarette smoking were less than those achieved in the MRFIT, but serum cholesterol differences were appreciably greater.<sup>11</sup> An overall impression from this partial review, particularly of recent clinical trials, is that the interventions used in the MRFIT would be expected to have a beneficial effect. However, sufficient differences from MRFIT exist in study design and related factors that firm conclusions are not possible.

The second possible explanation for the nonsignificant mortality outcome in the MRFIT is that the hypothesis received a less than definitive test, and the observed differences in mortality represent chance deviations from a larger effect that this intervention program has in the population. We have noted earlier that the power of the trial was lower than projected. One way to consider this problem, now that the trial has been completed, is through the 90% CI for CHD mortality. This ranged from a

favorable effect of 25% to a harmful effect of 15%, an interval that includes the 22% benefit projected from the observed risk factor changes. A related approach is to compute the probability of observing a CHD mortality rate differential of 7.1% or less, given the observed mortality rate in the UC (19.3 deaths per 1,000) and the mortality reduction projected from the observed risk factor reduction (22%). This probability is .12, indicating that the observed result is not inconsistent with a hypothesized 22% mortality differential; however, it suggests that an effect of this magnitude is unlikely.

The third possible explanation, that some aspect of the intervention program has a deleterious effect on mortality in some subgroups, has been extensively investigated. Thus, we observed that the men who stopped smoking cigarettes were considerably less successful in weight control than were men who continued to smoke,<sup>1</sup> yet against any important negative influence was the finding that weight reduction was greater, overall, for SI than UC men.<sup>1</sup> Also, diuretics seem to increase the level of plasma cholesterol, and men who took such drugs (including nearly all hypertensive men in the SI group) had a blunting of the dietary hypocholesterolemic effect such that they achieved only about half of the cholesterol-lowering seen in men not receiving these drugs and a modest elevation of plasma triglyceride levels.<sup>12</sup> While it might be reasonable to conclude that a lessened lipid-lowering might mean a lessened improvement in CHD, CVD, and total mortality, one could hardly conclude that this effect actually increased mortality.

Another possibility, namely, that other aspects of drugs used in the treatment of hypertension in MRFIT contributed to an increased mortality, was explored. It was noted that among those hypertensive at baseline (and therefore most likely to have antihypertensive drug therapy), intervention did not result in an appreciable difference in number of deaths from CHD in the two groups (80 SI deaths and 79 UC deaths). When examined further, it seemed that the largest percentage increase in CHD mortality for SI compared with UC occurred in men with hypertension at entry whose baseline resting ECGs

showed signs of abnormalities. These findings are not conclusive, but the possibility that the use of pharmacologic therapy in these subgroups is associated with an increased CHD mortality warrants further investigation.

In some contrast with the ambiguous but disquieting results in those with hypertension are the findings in other subgroups. Here again, we mention that such subgroup data are cited with awareness of their limitations and to indicate trends and avenues for future study. Among those not hypertensive at baseline, but of course possessing other risk factors, there were 35 deaths from CHD in the SI men and 45 deaths in the UC group. Furthermore, examination of the mortality data for men with serum cholesterol values of 250 mg/dL or more at the first screening visit, but without hypertension, revealed 18 deaths from CHD in the SI group and 33 in the UC group. Similarly, among those who were cigarette smokers at baseline but were not hypertensive, there were 31 coronary deaths in the SI category and 40 among the UC men. There is therefore a pattern, at least for CHD mortality, suggesting that among those MRFIT men free of hypertension at baseline, life-style changes may result in favorable reductions in mortality.

Thus, of the possible interpretations of the mortality results, the last discussed—a combination of favorable and unfavorable effects of the intervention program—seems most plausible. Even with the unexpected sizable risk factor reduction among the UC men, the lower-than-expected UC mortality, and the duration of intervention averaging only seven years, the likelihood that these factors resulted in missing an overall positive effect is relatively low. The data suggest that, except for some groups of hypertensive persons, particularly those with resting ECG abnormalities, the MRFIT intervention is apparently associated with a lower CHD mortality in the SI group.

## CONCLUSION

In conclusion, we have shown that it is possible to apply an intensive long-term intervention program against three coronary risk factors with considerable success in terms of

risk factor changes. The overall results do not show a beneficial effect on CHD or total mortality from this multifactor intervention. These results are accompanied by an apparent heterogeneity of effects among sizable subgroups, but there must be caution in reaching conclusions from such subgroup data. It may be relevant that multifactor intervention received a less than optimal test owing, in part, to unexpected declines in risk factor levels and, in part, to lower-than-expected mortality in the UC group. In regard to the former, the UC men thus constituted to a considerable extent a "treated" group.

The SI-UC comparisons indicate that among men with normal baseline ECGs, the MRFIT intervention program may have had a favorable effect on CHD mortality. The data also suggest that men with hypertension, primarily those with resting ECG abnormalities, had no favorable, and possibly an unfavorable response to intervention. More study is required to clarify this issue and its possible relation to antihypertensive treatment. Findings also include the within-group observation that men who stopped cigarette smoking had lower CHD and total mortality than those who continued to smoke.

The results of this trial do not address the possible effects of risk-factor intervention carried out over time periods of a decade or more or those begun before middle age. Future publications will address the morbidity results of the trial, subgroup hypotheses, and the role of other major variables.

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# Predicting Death From Renal Failure in Primary Hypertension

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After a retrospective study of 174 individuals who died from chronic primary hypertension, it was found that prediction of death from renal failure could be quantitated on the basis of initial measurement of the systolic blood pressure, cardiac-thoracic ratio, blood urea, and age at the time of initial diagnosis. The group with renal failure had massive cardiomegaly and very contracted kidneys. One half of the population was Negro, but the natural history of their hypertension was not convincingly different from the white group. If initial clinical observations are substituted in the discriminant equation,  $D = -1.5(\text{age at onset}) + 3(\text{percent cardiac-thoracic ratio}) + 0.5(\text{systolic blood pressure}) + 1(\text{blood urea})$ , and  $D$  is greater than 249, 85% of patients died of renal failure. If  $D$  is less than 249, 85% of patients died of causes other than renal failure.

The purpose of this investigation is to establish criteria, based upon information which can be readily obtained early in the course of primary hypertension, which will enable the clinician to predict which individuals will ultimately die of renal failure. With this end in mind, we studied the postmortem findings of patients dying of complications of hypertension and divided the group into those dying of renal failure and those dying of other causes. The initial clinical information obtained when the diagnosis of hypertension was first made was then analyzed in an attempt to establish a means for identifying these individuals with primary hypertension who were destined to die of renal failure. The discriminant equation which we have

produced may be of value in clinical classification of patients with hypertension.

## Methods

Postmortem records from the University of Virginia Hospital concerning 181 consecutive patients who died in the years 1960 through 1967 and who suffered from primary hypertension were carefully examined for information concerning the patient's age at death, the weight and appearance of the kidneys, the heart weight (including the proximal 2 cm of the ascending aorta), the left ventricular thickness, and the cause of death. Seven persons, however, were discovered to have had lesions suggestive of inflammatory kidney diseases (eg, pyelonephritis or glomerulonephritis). In four of these persons, these diseases were thought by the pathologist to be the actual cause of death, while in three persons

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they were considered to be an accompanying factor. Since it was believed that these diseases represented clinically diagnosable causes of secondary hypertension, all seven persons were removed from the study, thus leaving 174, 36 of whom died of renal failure. The only change in the data when these cases were deleted was an increase in the mean heart weight.

Clinical histories, obtained from both the hospital and outpatient clinic records, were also carefully examined for each person in the study. The usual manner for recording blood pressure at this hospital is with the patient sitting, after an interval of five to ten minutes. Hypertension was defined as a diastolic blood pressure equal to or greater than 90 mm Hg on at least two occasions or equal to or greater than 95 mm Hg on one occasion. Multiple readings, when recorded, were averaged by the investigators. Heights and weights were converted into the corresponding ponderal indexes (height in inches/cube root of weight in pounds). Blood urea and blood creatinine levels were determined by the methods of Skeggs<sup>1</sup> and of Chasson et al,<sup>2</sup> respectively. Cardiac-thoracic ratios (widest transverse diameter of the heart/widest transverse diameter of the thoracic cavity taken just above the level of the dome of the diaphragm) were measured from large x-ray films of the chest taken with the patient upright during full inspiration.

For all variables measured, means and standard deviations were calculated. The significance of differences between means was tested by the Student's *t* test. Discriminant functions<sup>3</sup> and regression analyses<sup>4</sup> were computed by the usual methods. Since both these techniques require that all data on each variable be present, any case with missing observations was discarded for that particular analysis. The numbers of patients actually used in the analyses are indicated in the Tables. The occurrence of missing data in the patient charts was quite random, so omission of incomplete records does not appear to introduce any bias.

## Results

The entire population consisted of 174 patients, all of whom suffered from primary hypertension. Classification by race and sex is found in Table 1. Negroes, both men and women, constituted the largest seg-

ment of those dying of renal failure, while white women constituted the smallest segment.

The major cause of death in the control group was cerebrovascular accidents (73 persons). Fifty-three persons died of cerebral hemorrhage and 20 of brain infarction. Myocardial infarction, the next most common cause, accounted for 29 deaths. Diabetes mellitus and congestive heart failure each accounted for 16 deaths, while aortic aneurysms were responsible for 13 deaths. Some other causes of death were pulmonary emboli (four), cancer (four), septicemia (three), cardiac arrhythmias (three), and mesenteric artery thrombosis (two). In several cases, multiple causes of death were listed for this control group. Renal failure was the cause of death in each of the 36 persons in the study group. Of this series of hypertensive individuals, 20.5% (7 in the group with renal failure and 29 in the control group) had a history of diabetes mellitus.

Examination of the pathologic data for those persons dying of renal failure revealed striking and significant differences with regard to age at death, heart weight, and kidney weight when compared to data for the control group (Table 2). Those persons dying of renal failure died ten years younger than did those dying of other causes. The mean age at death for group with renal failure was 52 years, while for the control group it was 62 years ( $t = 4.35$ ,  $P < 0.001$ ).

While both groups demonstrated substantial cardiac hypertrophy, those dying of renal failure had a much greater degree of hypertrophy. The mean heart weight for the group with renal failure was 607 gm, while for the control group it was 503 gm ( $t = 3.96$ ,  $P < 0.001$ ).

The last substantial difference between these two groups was the weight of the kidneys which averaged 112 gm for the group with renal

failure and 150 gm for the control group ( $t = 4.24$ ,  $P < 0.001$ ). The kidneys in the group with renal failure were generally contracted and shrunken with a granular appearance on gross inspection. Microscopic examination revealed evidence of arteriolar nephrosclerosis.

The thickness of the left ventricle was also measured in both groups. The mean was 19 mm for the group with renal failure and 17 mm for the control group. Because of the possibility of slight inconsistencies in measurement, we believe that not too much importance can be attached to this difference even though the difference is significant.

An examination of the clinical variables (Table 3) also reveals important differences between the two groups, especially with regard to the age at onset, initial systolic blood pressure, initial cardiac-thoracic ratio, and initial blood urea level. The mean age at onset of hypertension was 46 for the group with renal failure and 54 for the control group ( $t = 3.20$ ,  $P = 0.001$ ).

The mean initial systolic blood pressure for the group dying of renal failure was 212 mm Hg, while for the control group it was 190 mm Hg ( $t = 2.80$ ,  $P = 0.003$ ). The mean initial cardiac-thoracic ratio was 58% for the group with renal failure but only 53% for the control group ( $t = 2.51$ ,  $P = 0.008$ ). The mean initial blood urea level for the group with renal failure was 135 mg/100 ml, while for the control group it was 45 mg/100 ml ( $t = 5.95$ ,  $P < 0.001$ ).

Blood creatinine levels were also recorded, but the sample size was much smaller in the control group since this test was generally performed only when renal malfunction was suspected. Ponderal indexes were recorded but no substantial differences between the two groups were observed. This statement holds true for the initial diastolic blood pressure, as well. Finally, duration

Table 1.—Characteristics of Hypertensive Population

	Deaths, No.	
	Renal Failure	Other Causes *
White		
Men	7	48
Women	3	26
Negro		
Men	13	31
Women	13	33
Total	36	138

\* Some of these causes of death were cerebral hemorrhage (53), brain infarction (20), myocardial infarction (29), congestive heart failure (16), and diabetes mellitus (16).

of the illness was calculated for all those persons in whom the diagnosis of hypertension was made for the first time at the University of Virginia Hospital. It was shown that persons in the group with renal failure, though younger, lived an average of 5.0 years after the diagnosis was made, while those in the control group died an average of 7.5 years later ( $t = 2.07$ ,  $P = 0.03$ ).

No single variable cleanly separated those who would die of renal failure from the rest. For example, although the blood urea level was much higher in the group with renal failure, it was also elevated in many of the controls. Since many of the variables are intercorrelated, the impact of all variables taken together is difficult to assess. Discriminant analyses with several different sets of variables were therefore performed on those patients for whom we had complete data to determine whether the two groups could be more clearly differentiated on the basis of optimally weighting the clinical variables which had been measured early in the course. The advantage of using a discriminant score is that several clinical variables and their complex interrelations are reduced to a single, easily understood number. The best result is shown in Table 4. Although only 49 cases with complete data were available for this analysis, the results are highly significant.

Each of the four clinical variables

Table 2.—Means  $\pm$  Standard Deviations of Pathologic Data for Entire Population

	Death by Renal Failure				Death by Causes Other Than Renal Failure			
	Entire Group		Whites *	Negroes *	Entire Group		Whites *	Negroes *
	Means $\pm$ SD	Sample Size	(10), Means	(26), Means	Means $\pm$ SD	Sample Size	(74), Means	(64), Means
Age at death	52.1 $\pm$ 10.0	36	55.5	50.7	61.7 $\pm$ 12.2	138	61.0	62.4
Heart weight, gm	607.1 $\pm$ 136.4	34	620.0	601.7	503.2 $\pm$ 137.3	138	487.8	521.1
Left ventricular thickness, mm	19.2 $\pm$ 3.5	33	19.8	18.9	16.8 $\pm$ 4.1	129	16.2	17.4
Mean kidney weight, gm	111.6 $\pm$ 34.7	33	117.0	109.5	149.9 $\pm$ 49.0	136	154.8	143.4

\* Sample sizes for individual variables may be slightly smaller because of missing data.

Table 3.—Means  $\pm$  Standard Deviations of Clinical Data for Entire Population

	Death by Renal Failure				Death by Causes Other Than Renal Failure			
	Entire Group		Whites *	Negroes *	Entire Group		Whites *	Negroes *
	Means $\pm$ SD	Sample Size	(10), Means	(26), Means	Means $\pm$ SD	Sample Size	(74), Means	(64), Means
Age at onset	46.2 $\pm$ 9.3	26	48.3	45.6	54.4 $\pm$ 12.0	84	54.7	54.1
Initial systolic BP, mm Hg	211.8 $\pm$ 44.3	28	222.8	208.2	190.3 $\pm$ 30.8	77	189.2	191.2
Initial diastolic BP, mm Hg	118.5 $\pm$ 20.6	28	122.6	117.2	113.1 $\pm$ 16.4	77	113.1	113.0
Initial cardiac-thoracic ratio	58.4 $\pm$ 6.7	17	54.3	59.7	53.4 $\pm$ 6.8	36	50.2	55.0
Initial urea level, mg/100 ml	135.2 $\pm$ 105.6	27	189.7	116.2	45.1 $\pm$ 40.2	65	47.4	43.7
Highest urea level, mg/100 ml	488.6 $\pm$ 173.4	30	508.7	483.5	94.4 $\pm$ 73.2	100	86.1	101.9
Last urea level, mg/100 ml	465.1 $\pm$ 181.7	30	498.0	456.9	71.8 $\pm$ 49.3	108	68.2	75.3
Initial blood creatinine, mg/100 ml	7.8 $\pm$ 5.6	18	9.0	7.3	2.3 $\pm$ 1.2	9	2.6	2.0
Highest blood creatinine, mg/100 ml	20.7 $\pm$ 7.2	18	22.5	20.2	2.7 $\pm$ 1.7	36	2.6	2.8
Last blood creatinine, mg/100 ml	18.4 $\pm$ 8.3	18	21.8	17.4	2.3 $\pm$ 1.4	36	2.2	2.4
Ponderal index	12.0 $\pm$ 0.8	25	12.2	11.9	12.1 $\pm$ 1.1	74	12.3	11.9
Duration, yr	5.0 $\pm$ 3.6	26	2.3	5.8	7.5 $\pm$ 5.8	84	7.4	7.6

\* Sample sizes for individual variables may be smaller because of missing data.

Table 4.—Discriminant Analysis Based on Initial Clinical Findings \*

Variables	Age at Onset	Initial CTR, % †	Initial Systolic BP, mm Hg	Initial Blood Urea, mg/100 ml
Mean values				
14 dying of renal failure	46.7	58.9	214	106
35 dying of other causes	53.9	53.5	196	37
Significance tests				
Discriminant coefficient	-0.0015	0.0031	0.00047	0.0011
t test on coefficient	-1.77	2.13	1.65	5.25
Probability (44 df)	<0.05	<0.025	<0.1	<0.001

\* Analysis of variance for discrimination:  $F_{4,44}$  ratio = 12.02,  $P < 0.001$ .

† CTR = cardiac-thoracic ratio.

(initial blood urea level, age at onset, initial cardiac-thoracic ratio, and initial systolic blood pressure) contributed in varying degrees ( $P < 0.001$ ,  $P < 0.05$ ,  $P < 0.025$ , and  $P < 0.1$ , respectively) to the differentiation of the group with renal failure from the control population. The  $F$  ratio for the discriminant function was 12.02 ( $P < 0.001$ ), and this indi-

cates the differences in the discriminant scores could hardly have occurred by chance.

This discriminant equation (Table 4) was then applied to the original data for the purpose of determining prognosis. As is the usual custom, the discriminant coefficients were multiplied by a constant (in this case, 1,000) to avoid the use of cum-

bersome decimals. The simplified equation was as follows:  $D = -1.5$  (age at onset) + 3 (initial cardiac-thoracic ratio) + 0.5 (initial systolic blood pressure) + 1 (initial blood urea). Note that age of onset has a negative coefficient since older people tended to die of other causes; the other three have positive coefficients, since they favor death from renal failure. The coefficients essentially are an optimal mathematical estimate of how much each piece of initial clinical information should be weighted. Those who use the blood urea nitrogen level can substitute 2.1 (initial blood urea nitrogen) for the last term in the equation.

The discriminant scores for the group with renal failure ranged from 221 to 471 (mean, 325;  $SD = 75.6$ ), while the control group scores ranged from 134 to 287 (mean, 216;

Table 5.—Regression Analysis of Kidney Weight Versus Other Initial Clinical Variables \*

Variables	Systolic BP, mm Hg	Pulse Pressure, mm Hg
Kidney weight		
Regression coefficient (b)	-0.435	-0.480
Intercept (a)	217.3	174.5
Significance tests		
F <sub>1,99</sub> Ratio	12.25	8.56
Probability	<0.001	<0.005

\* Number of cases = 101. Regression equation is kidney weight = a + b (variable).

SD, 32.1). Thus in these patients if the score was less than 221, the patient was certain to die of other causes, and if the score was greater than 287, the patient was certain to die of renal failure.

With scores in the region of 221 to 287, a definite prognosis could not be made. At a score of 230, one third of those expected to die of renal failure did die of other causes, while at 250 only 14% died of other causes and at 275 only 3% died of other causes. The minimum misclassification is at a cutoff point of 249, where 15% of those above 249 died of other causes, and 15% of those below 249 died of renal failure. (This point is usually obtained by bisecting the Mahalanobis distance between populations,<sup>5</sup> but in this case, since the variances of the two groups were different, the point was obtained by working directly with the standard deviations of the two groups.)

Both single and multiple regression analysis was also performed, with the above four variables as well as the mean arterial pressure and the systemic pulse pressure, in attempts to predict final kidney weights. The best fit for a single independent variable was found to be an inverse relation between initial systolic blood pressure and the mean kidney weight at autopsy (Table 5); although a wide initial pulse pressure also tended to indicate that the terminal kidney size would be small.

#### Comment

The occurrence of cardiac hypertrophy with contracted kidneys was first documented well over 100 years ago by Bright:

It is observable, that the hypertrophy of the heart seems, in some degree, to have kept pace with the advance of the disease in the kidneys.<sup>1</sup>

Since this discovery, many investigations have been conducted into the relationship between cardiac hypertrophy, hypertension, and renal disease,<sup>7-10</sup> a substantial proportion of them concerned with the classification and description of malignant hypertension. Given the relatively young age of the patients at onset of hypertension and the predominance of Negroes in our group with renal failure, the question naturally arose as to whether or not we were dealing simply with a group of individuals who suffered from malignant hypertension. Several important facts, however, militate against such a conclusion.

Descriptions of kidneys removed during postmortem examinations of persons who had malignant hypertension have shown that these kidneys vary from slightly below normal weight,<sup>11</sup> (130 gm,<sup>12</sup> 139 gm<sup>9</sup>) to normal or slightly greater than normal,<sup>14</sup> with few exceptions.<sup>10</sup> In contrast, the kidneys from our group with renal failure were markedly contracted and decreased in weight (111 gm). The mean duration from the time of diagnosis of hypertension to death in our group with renal failure was 5.0 years, compared with durations in persons with malignant hypertension ranging mostly from one month to two years.<sup>9-11,17</sup> Cardiomegaly, while an extremely common accompaniment in malignant hypertension, has rarely been recorded at the level found in our population with renal failure (607 gm),<sup>9,10,15,17</sup> probably because of the shorter duration of malignant hypertension. Finally, our population with renal failure had only a slight predominance of men over women. For

Negroes, the number in both sexes was identical, which contrasts with the predominance of males found in studies of malignant hypertension and recorded as 3:2,<sup>9,15</sup> 2:1,<sup>12</sup> and greater.<sup>16</sup>

While we were unable to confirm the findings of investigators such as McDonough et al,<sup>20</sup> Saunders and Bancroft,<sup>21</sup> or Comstock<sup>22</sup> that Negroes have higher blood pressures than whites (Table 3), we did discover a much higher proportion of Negroes than whites with severe hypertension who died of renal failure (26 Negroes and ten whites in a hospital whose population is 45% Negro). It is possible that once severe hypertension is established, racial differences in blood pressure become obscured by the common course of the disease.

Despite the measurement of 16 variables, significant ( $P \leq 0.05$ ) racial differences within each of the two groups were found in only four variables; heart weight, kidney weight, and cardiac-thoracic ratio in the control group and duration of disease in the group with renal failure. These small differences, however, cannot account for the much larger differences observed between the two groups. Similarly, even smaller differences between men and women cannot account for the large differences.

The predominance of Negroes in our renal failure group does, however suggest that there may be a racial difference in the susceptibility of the renal vascular bed to sclerosis. The fact that regression analysis demonstrated decreased kidney weight at autopsy to be associated with both an initial increased systolic blood pressure and pulse pressure, and the fact that the Negroes in our group with renal failure had slightly lower systolic blood pressures than did the white persons might further support the hypothesis of their increased susceptibility to renal sclerosis.

We cannot explain the extreme degree of cardiomegaly observed in our group with renal failure. That this group did in fact respond with greater hypertrophy, not simply dilation, than did our control group, is attested to by the much greater cardiac weight and the slightly greater left ventricular thickness in the group with renal failure.

This series obviously represents a highly selected population. The obvious bias in the selection of our population is that it represents a group of people who suffered from severe hypertension, a conclusion supported both by the mean blood pressures of both groups and by the fact that these people were sick enough to be brought to a hospital just prior to death. This bias might also account for the very high proportion of individuals who died of cerebrovascular accidents in our control population. We can only guess at the extent of these biases, comment on the difficulties of retrospective studies of hospital records due to lack of uniform recording of information and missing data, and suggest that a prospective study of primary hypertension is indicated.

The discriminant equation could be a valuable tool in predicting prognosis for hypertensive patients, since easily measured clinical indexes are used. Although this clinic and hospital population is obviously a select group, the selection bias at this institution is similar to those in other hospitals. Thus these equations probably would be reasonably accurate if applied to other clinic populations. Further, the use of discriminant functions assumes there is a linear relation among the variables and that the data is normally distributed. These seem to be reasonable assumptions. To demonstrate calculation of the discriminant score, we have selected a typical patient from each group for sample calculations using the coefficients of Table

4:  $D = -1.5(\text{age at onset}) + 3(\text{initial cardiac-thoracic ratio}) + 0.5(\text{initial systolic blood pressure}) + 1(\text{initial blood urea}).$

Case 34 is that of a Negro man who died of renal failure and had a score greater than 249. His condition was diagnosed as hypertension at this hospital when he was 51 years old. At that time, his systolic blood pressure was 230 mm Hg. An x-ray film of the chest revealed a cardiac-thoracic ratio of 62%, and his blood urea level was found to be 52 mg/100 ml. Therefore  $D = -1.5(51) + 3(62) + 0.5(230) + 52 = 353$ .

Case 142 is that of a white man who died of a ruptured aortic aneurysm and had a score of less than 249. His condition was diagnosed as hypertension at the age of 66. His systolic blood pressure was 210 mm Hg; his cardiac-thoracic ratio, 50%; and his blood urea level, 44 mg/100 ml. Therefore  $D = -1.5(66) + 3(50) + 0.5(210) + 44 = 200$ .

In conclusion, according to our study, the individual with severe primary hypertension who is likely to die of renal failure is a man of either race or a Negro woman, about 45 years of age, with a high blood pressure, especially systolic, marked cardiac enlargement as determined by the cardiac-thoracic ratio, and an elevated blood urea level. Such a person will probably die within about five years with extreme cardiomegaly and markedly contracted kidneys. These patients might represent a distinct entity within the catchall referred to as primary hypertension.

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## Predicting Risk of Ischemic Heart Disease and Cerebrovascular Disease from Systolic and Diastolic Blood Pressures

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The relative importance of systolic versus diastolic blood pressure in predicting risk of ischemic heart disease or cerebrovascular disease is controversial. Since 1948 we have observed in the Manitoba Study 3983 men (most between 25 to 34 years old at entry), in whom risk of both diseases was determined using the multiple logistic model. Systolic and diastolic blood pressures after adjustment for age and body weight were compared at entry and at four other examinations during the follow-up period. When both blood pressures were considered together, a stronger association with cerebrovascular disease was found for systolic compared to diastolic blood pressure at entry and at most of the other examinations. For ischemic heart disease, diastolic pressure showed a stronger association at the earlier examinations, whereas systolic pressure was more important when the majority of the cohort was between 40 to 50 years of age. In middle-aged men the general concept that diastolic is more important than systolic is not justified for cerebrovascular disease or for ischemic heart disease.

BLOOD PRESSURE has been identified as a powerful predictor for the occurrence of ischemic heart disease (1-13) and cerebrovascular disease (14-19). Whether systolic or diastolic pressure is more important as a risk factor for these diseases has been debated. Clinical teaching (20, 21) and the attitude of many physicians is that diastolic is more important. For ischemic heart disease many epidemiologic studies (1, 3, 7-13) favour systolic and for cerebrovascular disease, a single study (19) favours systolic.

Another aspect of this controversy is the suggestion in the Framingham data (9) that diastolic blood pressure is a more important predictor of ischemic heart disease in those less than 45 years of age at entry, whereas in older age groups systolic is more important. These findings, however, could not be confirmed by the Western Collabora-

tive Group study (13). If age is a relevant consideration most prospective cardiovascular studies may be unable to evaluate completely the relation between age at measurement of blood pressure and ischemic heart disease risk because they consist primarily of middle-aged people. The Manitoba Study, however, provides a better opportunity to examine this question because it consists of a cohort of North American men who were predominantly between 25 to 34 years on entry and have been followed into their middle-aged years.

### Methods

The details of this study have been reported previously (22-24). In summary, the cohort consists of 3983 subjects, who during World War II were either pilots or pilots-in-training in the Royal Canadian Air Force or pilots licenced by the Department of Transport; at that time they had a routine electrocardiogram in addition to the regular medical examination. After release from the Service, a few continued to fly, but the majority found different occupations and are in all strata of society.

For each subject, measurements of age, blood pressure, body weight and height at the examination closest to 30 June 1948 (date population was defined) were selected as the entry examination. Earlier medical information and examinations provided evidence that they were without clinical manifestations of ischemic heart disease or cerebrovascular disease when the population was defined. At entry the age distribution, was 318 for ages 15 to 24 years; 1479, 25 to 29 years; 1258, 30 to 34 years; 539, 35 to 39 years; 205, 40 to 44 years; 153, 45 to 54 years; and 31, 55 to 64 years. Since then they have been followed by annual mail contact and periodic examinations of at first 5 and later 3 years. Annual contact has been lost with only one person. The observation period was defined from 1 July 1948 until 30 June 1974, an average follow-up of 26 years. Because of blood pressure changes after entry (23) several other examinations at 5 year intervals were also considered—those closest to 30 June 1954, 1959, 1964 and 1969.

Men prescribed antihypertensive medications were included in the analysis because of their relatively small number and difficulties in assessing their compliance with therapy. The numbers of persons known to be on antihypertensive drugs who developed ischemic heart disease, cerebrovascular disease, or were free of both were respectively: nine, nine, and 83 by 1969; 10, five and 23 by 1964; nine, three, and nine by 1959; one, one, and two by 1954; and none in 1948 at entry.

► From The University of Manitoba Follow-up Study, Department of Medicine, and the Department of Social and Preventive Medicine, University of Manitoba; Winnipeg, Canada.

Table 1: Multiple Logistic Function Standardized Coefficients Relating Risk of Ischemic Heart Disease (IHD)\* to Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) after Adjusting for Age and Body Mass Index

Variable	1948-1974†/1948‡		1954-1974/1954		1959-1974/1959		1964-1974/1964		1969-1974/1969	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Both SBP and DBP	0.0830	0.2857§	-0.0071	0.2515§	0.0918	0.2155§	0.2234	0.1394	0.2911	0.1082
SBP only	0.2427§		0.1508§		0.2339§		0.3233§		0.3682§	
DBP only		0.3328§		0.2469§		0.2757§		0.2956§		0.3126§
Mean age at examination $\pm$ SEM, yrs										
IHD	35.1 $\pm$ 0.4		40.2 $\pm$ 0.4		44.4 $\pm$ 0.4		48.8 $\pm$ 0.4		53.0 $\pm$ 0.6	
No IHD	31.0 $\pm$ 0.1		36.9 $\pm$ 0.1		41.8 $\pm$ 0.1		46.7 $\pm$ 0.1		51.6 $\pm$ 0.1	
Cases, no.										
IHD	390		325		310		241		131	
No IHD	3593		3143		3435		3381		3259	

\* Missing observations are not included: For IHD there were 36 cases occurring after 1954 that were missing 1954 measurements; for 1959 there were 19; for 1964, 12; and for 1969, 8.

† Observation period.

‡ Year of examination.

§  $P < 0.01$ .

||  $P < 0.05$ .

### Incidence of Ischemic Heart Disease and Cerebrovascular Disease

During the 26-year observation period, 390 ischemic heart disease and 78 cerebrovascular disease cases were observed. The diagnostic criteria for heart disease have been reported previously (24), and the criteria for cerebrovascular disease are similar to those used by the coronary drug project (25). While the percentages of the various manifestations of both diseases vary in each time period, about 75% of heart disease cases had hard evidence consisting of myocardial infarction (52%) or sudden death (23%) and 65% of the cerebrovascular disease cases had hard evidence classified in the definite or probable category.

### Data Analysis

The multiple logistic function model (26) for determining ischemic heart or cerebrovascular disease risk was used to fit the data for systolic and diastolic blood pressure, body mass index (weight/height<sup>2</sup>), and age. This model was chosen for two reasons. Firstly, as stated by Rosenman, Shotz, and Brand (13) "traditional cross tabulation methods present difficulties in simultaneously dividing systolic and diastolic blood pressure into for example, tertiles for both systolic and diastolic risk and at the same time adjusting for other variables." Secondly, this approach has been widely used in assessment of ischemic heart disease risk (6, 8, 10, 11) and in studies that examined the relative contribution of systolic or diastolic blood pressure as a risk factor (9, 13, 19).

Because of differences in the usual range of values for systolic and diastolic blood pressure a direct comparison of the logistic function coefficients is not appropriate to determine the relative predictive strength of each blood pressure. For this reason each is standardized by its respective population standard deviation, a measure of its range. Thus the standardized coefficients (logistic function coefficients  $\times$  population standard deviation) (19) provide a direct method of comparison of the two blood pressures—the larger the standardized coefficient, the more important that pressure.

### Results

Table 1 shows the results of using the logistic model to predict ischemic heart disease when both blood pressures are considered simultaneously and separately. The mean age of the groups, with and without heart disease, at each examination is also provided. When both blood pressures were analyzed together, only diastolic was a significant predictor for the 1948, 1954 and 1959 examinations while only systolic was the significant blood pressure in 1964

and 1969. The mean age of the ischemic heart disease group in 1964 when this change in relative importance of systolic versus diastolic blood pressure occurred was  $48.8 \pm 0.4$  years ( $\pm$  SEM).

The value of the standardized coefficients showed a trend of decreasing magnitude for diastolic and increasing magnitude for systolic over the observation period. When systolic and diastolic were studied separately each was significantly related to ischemic heart disease incidence. The trend of increasing magnitude of the predictive power for systolic pressure with each subsequent examination was noted. Figure 1 shows that a steeper increase in the probability of developing ischemic heart disease can be seen for systolic blood pressure in 50-year-old men compared to 40-year-old men in 1964.

The results of the same analysis for cerebrovascular disease are shown in Table 2. A stronger association between blood pressure and cerebrovascular disease than for blood pressure and ischemic heart disease was observed as shown by the larger standardized coefficients for systolic and diastolic blood pressure in Table 2 compared with Table 1. Except in 1954, all examinations showed systolic more strongly associated with cerebro-

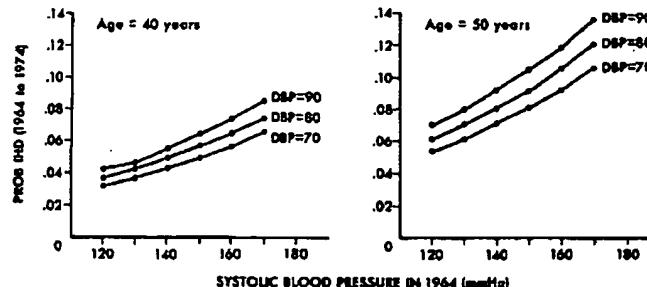


Figure 1. The probability of ischemic heart disease (PROB IHD) is shown based on the 1964 measurements for men aged 40 years (left) and 50 years (right) with the mean body mass index of each age. Without blood pressure measurements the probability of ischemic heart disease is 0.04 for 40 year olds and 0.074 for 50 year olds. Increasing levels of systolic (abscissa) or diastolic blood pressure (DBP) (curves) are associated with an increasing probability of disease. At the same levels of diastolic blood pressure increasing levels of systolic pressure have a greater increase in risk for 50 year olds (steeper slope of lines) compared to 40 year olds.

Table 2: Multiple Logistic Function Standardized Coefficients Relating Risk of Cerebrovascular Disease (CVD)\* to Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) After Adjusting for Age and Body Mass Index

Variable	1948-1974†/1948‡		1954-1974/1954		1959-1974/1959		1964-1974/1964		1969-1974/1969	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Both SBP and DBP	0.4506§	0.2452	0.1076	0.2891	0.7836§	-0.0053	0.9790§	0.4944§	0.8483§	0.2306
SBP only	0.5846§		0.2864**		0.7799§		1.3297§		1.0234§	
DBP only		0.4928§		0.3567§		0.4990§		1.1737§		0.8352§
Mean age at examination $\pm$ SEM, yrs										
CVD	39.4 $\pm$ 1.1		44.7 $\pm$ 1.3		49.0 $\pm$ 1.1		53.7 $\pm$ 1.2		57.0 $\pm$ 1.6	
No CVD or IHD††	30.9 $\pm$ 0.1		36.8 $\pm$ 0.1		41.8 $\pm$ 0.1		46.6 $\pm$ 0.1		51.5 $\pm$ 0.1	
Cases, no.										
CVD	78		57		67		53		32	
No CVD or IHD	3536		3097		3382		3331		3214	

\* Missing observations are not included: 12 CVD cases after 1954 were missing 1954 measurements.

† Observation period.

‡ Year of examination.

§  $P < 0.01$ .

||  $0.05 < P < 0.10$ .

\*\*  $P < 0.05$ .

†† IHD = ischemic heart disease.

vascular disease than diastolic because the standardization coefficients for systolic were larger than those for diastolic when both were analyzed together or separately. The greater relative importance of systolic compared to diastolic is more striking for cerebrovascular disease than for ischemic heart disease, as shown by the larger difference between the standardized coefficients between systolic and diastolic pressure for cerebrovascular disease.

The comparison group for ischemic heart disease were those who remained free of it during the observation period. For cerebrovascular disease, the comparison group were those who remained free of both diseases. The results are not significantly affected by this difference. For example, when both blood pressures are considered together and the comparison group is free of both diseases (as in Table 1), the standardized coefficients for ischemic heart disease risk are as follows respectively for systolic and diastolic pressure: 0.0936 and 0.2983 ( $P < 0.01$ ) in 1948; 0.002 and 0.2532 ( $P < 0.01$ ) in 1954; 0.1162 and 0.2097 ( $P < 0.01$ ) in 1959; 0.2475 ( $P < 0.05$ ) and 0.1466 in 1964; and 0.3235 ( $P < 0.05$ ) and 0.1085 in 1969. In a comparison group of men without cerebrovascular disease, the following standardized coefficients were determined for systolic and diastolic pressure when both were used together to predict cerebrovascular disease risk: 0.4264 ( $P < 0.01$ ) and 0.1990 in 1948; 0.0602 and 0.2614 in 1954; 0.7370 ( $P < 0.01$ ) and -0.0431 in 1959; 0.8746 ( $P < 0.01$ ) and 0.4924 ( $P < 0.01$ ) in 1964; and 0.7924 ( $P < 0.01$ ) and 0.2488 in 1969. Because ischemic heart disease is a risk factor for cerebrovascular disease in univariate analysis (10 of 52 versus 380 of 3931  $\chi^2 = 5.3$ ,  $P < 0.05$ ), such cases were excluded from prediction of cerebrovascular disease risk. However, in each of the last three examinations there were only about three cases with prior ischemic heart disease who later developed cerebrovascular disease. This small number prevented satisfactory analysis of its potential contribution. Nevertheless including it as a variable in the logistic model did

not materially alter the standardized coefficients given above.

#### Discussion

The present analysis reinforces the generally accepted belief that casual blood pressure measurement is a predictor of or a risk factor for ischemic heart disease and cerebrovascular disease (1-19). Recognizing that either systolic or diastolic pressure may be used for predicting the risk of both diseases, the primary purpose of this report was to examine the comparative value of each blood pressure. For ischemic heart disease we have noted (24) the dominant role of diastolic pressure at the entry examination of this cohort. In this study diastolic pressure is found to have a predominant role at the earlier examinations but after the cohort's mean age was more than 45 years the relative importance of diastolic declined while that of systolic increased. This confirms the findings in the Framingham data (9). The stronger association of systolic than diastolic blood pressure with cerebrovascular disease is consistent with other epidemiologic (19) and pathologic (27) studies.

The limitations of the present study are that this cohort is a highly selected one and data on other important factors such as cholesterol and cigarette smoking are not available. However, the purpose of this report was to compare systolic and diastolic blood pressure. The younger ages at entry in this cohort compared with most other cohorts permit better examination of the relation of ischemic heart and cerebrovascular disease and blood pressure in younger men.

Our observations provide an explanation why most epidemiologic studies that consider persons mainly in their mid 40's or older favour systolic over diastolic pressure (1-3, 7-13). Interestingly, the Evans County study (6) that favoured diastolic had 44% of its cohort less than 45 years of age at entry.

The reason for the changing relative importance of sys-

tolic and diastolic is uncertain. One explanation is that the greater variability of systolic, causing a larger standard error of its measurement, does not allow the statistical separation of the ischemic and nonischemic heart disease group. With aging, a proportionately greater increase in systolic than diastolic pressure occurs. The greater difference in mean systolic pressure between the groups compensates for the larger variance in the measurement of systolic blood pressure. Other explanations include the concept that in older persons an elevated systolic blood pressure may be a marker of atherosclerosis in larger arteries as well as a 'risk factor' thus enhancing its predictive power for atherosclerosis in critical vasculatures. A causal relationship between the different blood pressures and the genesis of atherosclerosis (28) or myocardial damage at different ages is also possible.

Despite the evidence that both systolic and diastolic blood pressure predict ischemic heart or cerebrovascular disease and that systolic may be a better predictor at some ages than diastolic, clinical teaching and practice has stressed the greater importance of diastolic blood pressure. The concept that systolic is less relevant has been labelled a myth (29) or a misconception (30). The reasons behind its development have been recently reviewed (13). This controversy is critically important because the level of diastolic, not systolic, blood pressure is frequently the current indication for the treatment of hypertension (21, 31). Further, most antihypertensive drugs are directed at diastolic pressure (30). The results of this and other studies suggest that the challenge now is to direct attention at systolic in addition to diastolic pressure (32), to develop better therapy for elevated systolic pressure and determine whether its reduction will decrease the prevalence of ischemic heart disease and improve the reduction in cerebrovascular disease incidence already obtained by current antihypertensive medication (31).

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## The Diastolic Blood Pressure in Systolic Hypertension

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Because antihypertensive therapy is effective in elderly patients with isolated systolic hypertension, attention has been focused on the systolic blood pressure as a predictor of cardiovascular risk. However, it is a normal diastolic pressure that separates patients with isolated systolic hypertension from those with essential hypertension. The normal diastolic and elevated systolic pressures are largely due to age-related stiffening of the aorta. An indistensible aorta causes the pressure pulse to travel faster than normal, where it is quickly reflected off the peripheral resistance. The reflected wave then returns to the central aorta in systole rather than diastole. This augments the systolic pressure further, increasing cardiac work while reducing the diastolic pressure, on which coronary flow is dependent. The potential harm of further reducing the diastolic pressure with antihypertensive therapy, especially in patients with coronary heart disease, underlies the controversial "J curve." By decreasing the blood pressure, all antihypertensive agents improve aortic distensibility, but no agents do so directly; the nitrates come the closest. Such an agent would be useful because any therapeutic increase in aortic distensibility would decrease systolic pressure without greatly reducing diastolic pressure. The problem is complicated by the suspected inaccuracy of the cuff technique in predicting the aortic diastolic pressure. New noninvasive methods to predict the aortic diastolic pressure may help in the future. At present, the combination of a high systolic and normal diastolic pressure—a widened pulse pressure—seems to be the best predictor of cardiovascular risk in patients with hypertension or heart disease. Patients with isolated systolic hypertension should be treated, but marked diastolic hypotension should be avoided.

The prevalence of isolated systolic hypertension increases with advancing age, and it is now estimated that 20% of persons 75 years of age are affected (1). Therefore, as the population ages, the number of patients with the disorder will rise, making it an increasingly frequent clinical problem. For obvious reasons, emphasis has been placed on systolic blood pressure in isolated systolic hypertension, but consideration of the diastolic blood pressure may offer greater insight into the disease.

In 1927, Fineberg (2) first divided hypertensive patients into systolic and diastolic groups. Over the ensuing years, opinions about what is now called isolated systolic hypertension have changed markedly. Initially, it was considered a nondisease, a natural consequence of aging that was unworthy of therapy. Later, it was shown to have an associated mortality rate higher than that among persons of the same age without elevation of systolic blood pressure (3, 4). At that time, conventional wisdom held that antihypertensive treatment in patients with isolated systolic hypertension was risky because reducing the systolic blood pressure might induce stroke in patients who also had subclinical cerebrovascular disease (5). These fears were allayed by the findings of the Systolic Hypertension in the Elderly Program (SHEP) study (6) and Systolic Hypertension in Europe Trial (7), which showed unequivocal benefit from decreasing the blood pressure in patients with isolated systolic hypertension by using hydrochlorothiazide or the long-acting calcium-channel antagonist nitrendipine. Since the publication of the reports of these trials, attention has been largely directed to the systolic blood pressure. However, far less has been written about the normal or low diastolic blood pressure that separates patients with isolated systolic hypertension from those with essential hypertension.

The first issue is whether the cuff method for measuring the diastolic blood pressure is accurate in patients with isolated systolic hypertension. Although considerable scatter always results when cuff pressures are compared with intra-arterial brachial artery pressures, no systematic error has been found in comparisons of systolic blood pressure (8). By contrast, when disappearance of the Korotkoff sounds (phase V) is used, cuff diastolic pressures are consistently higher than intra-arterial pressures

by 10 to 15 mm Hg in patients with isolated systolic hypertension, those with peripheral atherosclerosis, and elderly persons (8-10). Therefore, the intra-arterial brachial artery diastolic pressures are even lower than the "normal or low" values used as entry criteria for recent studies of isolated systolic hypertension.

An even more vexing question is how well cuff pressures represent central aortic pressures, against which the heart must pump in systole and on which the coronary flow depends in diastole. Direct comparisons of cuff brachial artery pressures with those of the ascending aorta have not been made in patients with isolated systolic hypertension and would be difficult in this group because of the necessarily invasive nature of direct aortic pressure measurements. Other techniques for indirect measurement of aortic pressure are available, such as applanation of the carotid artery (11) or transfer functions from the carotid or even a more peripheral artery (12, 13), but the accuracy of these methods might still be in question among patients with isolated systolic hypertension because of the variability in the measurements and the inhomogeneous changes in the arterial walls that occur with aging.

Because most patients with isolated systolic hypertension are elderly and because the central aorta is known to stiffen with aging, the indistensible aorta provides a ready explanation for the high systolic blood pressure and low diastolic blood pressure in such patients (14). When the aorta is non-compliant, it is less able to stretch and accommodates even a normal stroke volume with a higher systolic blood pressure. As a consequence, more of the stroke volume is forced into the periphery during systole, leaving less blood in the arterial tree during diastole, which accounts for the lower diastolic blood pressure.

Another governing principle is that pressure waves travel faster through stiff pipes than through pliant ones. Therefore, pulse-wave velocity is faster in older persons, in whom the aorta is stiffer, than in younger persons. In both younger and older persons, these pressure waves are reflected off the peripheral resistance, which for the lower body can be localized to the level of the renal arteries (15). In younger persons, the waves that travel more slowly reach the reflecting sites and return to the central aorta at the end of systole or early diastole, at which point they amplify the mean diastolic pressure. Because the distance is shorter, reflections from the upper body reach the aorta first. With aging, reflected waves from the upper and especially the lower body travel faster and return to the central aorta in early to mid-systole, where they augment the already elevated systolic blood pressure and increase the work of the heart (16). These

reflected waves are the major cause of elevated systolic blood pressure, and thus the pulse pressure, in elderly persons. The amplitude of these wave reflections is even greater in hypertensive patients with elevated vascular resistance, the primary hemodynamic abnormality in essential hypertension. Loss of the reflected pulse augmentation in diastole reduces the mean diastolic pressure, the driving pressure for the coronary circulation, but has little effect on the minimal diastolic pressure recorded by the cuff method. These variations in aortic pulse wave shape were first described by Murgo and colleagues in 1980 (17). The pathophysiologic sequence of reduction in aortic distensibility is summarized and illustrated in the Figure in a pulse diagram (18).

The mechanisms described may account for the high prevalence of isolated systolic hypertension in elderly persons, but they fail to account for older persons who do not have the disease. Individual variations in the severity of aortic stiffening may be due to biological variability, environmental factors (19), or genetic factors (20). Accurate measurements of aortic distensibility are available (21, 22) and would help determine which patients have stiff aortas, but the studies are invasive and are not easily applicable to persons with isolated systolic hypertension. Further complicating the issue is that as a viscoelastic structure, the aorta stiffens with blood pressure elevation from any cause. Put another way, a stiff aorta could be the cause of systolic hypertension, the effect of essential hypertension, or both, and future measurements of aortic distensibility in isolated systolic hypertension will have to take the blood pressure itself into account as a variable.

The contribution of atherosclerosis to the aortic stiffening found with aging is easy to separate out in concept but is difficult in practice. In terms of hemodynamics, early atherosclerosis is a disorder of the arterial intima that has little effect on wall properties. However, aging stiffens the media, producing the pathological changes described above. Widespread, severe aortic atherosclerosis undoubtedly contributes to the loss of aortic distensibility to an undefinable extent when it coexists with the aging process. On the other hand, the medial stiffening found with aging probably plays little role in the genesis of atherosclerosis.

Even in the absence of atherosclerosis, other factors may influence the blood pressure in persons with a stiff aorta. Some patients with isolated systolic hypertension have high systemic vascular resistance, whereas others have a high stroke volume (23, 24), but neither of these conditions reduces the diastolic blood pressure. It is therefore likely that lack of aortic pliability is necessary but not always sufficient for the development of isolated systolic hypertension.

	Normal Aorta (Young Adults)	Stiff Aorta (Older Adults)	
1. Aortic BP (mm Hg)	130 80	Systolic Diastolic	140 70
2. PWV (m/s)	5.0		10.0
3. Reflected Wave	Early Diastole		Late Systole
4. Pulse Wave Shape			
5. Aortic BP (mm Hg)	130 80	Systolic Diastolic	160 70

**Figure. Development of aortic pressure abnormalities due to age-related aortic stiffening.** 1. Increased systolic blood pressure (BP) and decreased diastolic blood pressure due to decreased aortic distensibility. 2. Increased pulse wave velocity (PWV) as a result of decreased aortic distensibility. 3. Return of the reflected primary pulse to the central aorta in systole rather than diastole because of faster wave travel. 4. Change in the shape of the pulse wave because of early wave reflection. Note the reduction in diastolic pressure-time despite the increase in systolic pressure. Horizontal lines indicate systole; vertical lines indicate diastole. 5. The aortic blood pressure resulting from decreased aortic distensibility and early reflected waves. \* Primary reflected wave. Adapted from reference 18; pulse calibrations added by the authors.

High systolic blood pressure seems to be an obvious risk factor for stroke, increased left ventricular mass, and congestive heart failure. Whereas the mean blood pressure is the driving pressure for all other vascular beds, the diastolic blood pressure primarily drives the coronary flow. A low diastolic blood pressure, especially in the presence of coronary artery disease, may therefore explain the "J-curve phenomenon." The J curve has been described as an increasing cardiovascular risk when the cuff diastolic blood pressure is decreased by using antihypertensive therapy to less than 80 to 85 mm Hg (25-27). The expected decrease in diastolic blood pressure induced by therapy could be even greater in elderly persons with a stiff aorta and, as discussed previously in this paper, the aortic diastolic blood pressure may be even lower than that measured by the cuff method.

It is interesting that the initial fear of reducing the systolic blood pressure in patients with isolated systolic hypertension has proved to be unfounded, but our present concern may instead be excessive reduction of the diastolic blood pressure. The J-curve may be a bugaboo; it has not been found in a detailed retrospective observational study or a drug trial (28, 29). The drug trial, however, included only patients with diastolic hypertension ( $\geq 90$  mm Hg) whose average diastolic pressures decreased by only 5 to 6 mm Hg. The J curve was not discussed in

either the SHEP study or the Systolic Hypertension in Europe Trial, in which the diastolic blood pressure was clearly reduced to approximately the same extent. In a follow-up to the SHEP trial, no evidence of a J curve was detected (30). However, in a recent reanalysis of the SHEP data, a dose-response relation was seen in treated patients for more cardiovascular disease as the diastolic blood pressure decreased to less than 70 mm Hg (31). Nonetheless, the potential risk associated with a low diastolic blood pressure did not outweigh the favorable effects of reducing the systolic blood pressure.

The recently published Hypertension Optimal Treatment randomized trial (32) sought to identify the J curve but included only patients with elevations of diastolic blood pressure, and the results are therefore not applicable to patients with isolated systolic hypertension. Nonetheless, the results of the Hypertension Optimal Treatment trial regarding the J curve were equivocal; an observed increase in cardiovascular mortality with diastolic blood pressures less than 86 mm Hg was suggestive but not statistically significant. Interest in a low diastolic blood pressure has been heightened by information indicating that the wide pulse pressure found in hypertension is also a cardiovascular risk factor (33-35). This is true even among normotensive patients with left ventricular dysfunction after myocardial infarction (36), those with left ventricular dysfunc-

tion (37), and those in the Framingham Study population (38). In the Framingham Study, pulse pressure was the best predictor of cardiovascular risk, but at any given systolic pressure, an inverse relation was noted between diastolic pressure and coronary heart disease incidents. Although a wide pulse pressure is due less to a low diastolic blood pressure than to a high systolic blood pressure (39), the combination of the two, for reasons outlined here, could be the biggest risk factor in isolated systolic hypertension—the high systolic blood pressure increases the demand for left ventricular work, and the reduced mean diastolic pressure is a potential risk factor in patients with significant coronary heart disease.

If the J curve, a low diastolic blood pressure, and a wide pulse pressure are significant issues, how can an elevated systolic blood pressure be beneficially reduced in isolated systolic hypertension without adding the suspected risk for diastolic hypotension? Certainly, a normal baseline diastolic pressure in patients with isolated systolic hypertension should not dissuade clinicians from gaining the well-established benefits of prescribing antihypertensive therapy to decrease an elevated systolic blood pressure. Any agent that reduces peripheral resistance without changing the cardiac output will reduce the mean blood pressure and both the systolic and diastolic blood pressure, which oscillate around it.

Reduction of the mean blood pressure will improve aortic distensibility and narrow the pulse pressure by decreasing the systolic pressure more than the diastolic blood pressure. However, an ideal therapeutic agent in isolated systolic hypertension would have a direct relaxing effect on a stiffened aorta or the peripheral conduit arterial tree. Such an agent would decrease the systolic blood pressure and possibly increase the mean and even the minimum diastolic blood pressure by reversing the mechanisms described. Calcium-channel antagonists have such an action, as do angiotensin-converting enzyme inhibitors, but nitrates are among the best agents for relaxing the conduit arteries (40). If nitrates are effective in patients with isolated systolic hypertension, their mild effect on resistance vessels and peripheral veins would reduce the mean blood pressure, but if they increased arterial distensibility and changed the timing of reflected waves, systolic blood pressure should decrease and diastolic blood pressure should decrease less or increase—an ideal combination in these patients. Such changes would be best measured as surrogates of aortic pressure (by using carotid artery applanation or radial artery transfer functions), and if these changes are found, clinical studies of the effect of nitrates and other agents on aortic distensibility in small patient groups could be done. Although these ideas are

attractive in theory, little clinical evidence suggests that minimizing the reduction in diastolic pressure or even allowing it to increase during antihypertensive therapy is beneficial.

In summary, normal or low diastolic pressure is the defining characteristic that makes isolated systolic hypertension clinically different from essential hypertension. Understanding why the diastolic pressure is not also elevated requires some understanding of aortic distensibility and its loss with aging. Through several described mechanisms, increased aortic stiffness increases the systolic pressure but keeps the diastolic pressure normal or even a bit lower. The accuracy of cuff diastolic pressure is also a problem. In elderly persons and patients with isolated systolic hypertension, cuff systolic pressures fairly well represent intra-arterial brachial pressure and intra-aortic pressure. However, cuff-measured diastolic pressures systematically overestimate the intra-arterial brachial artery pressure. Whether the cuff or intra-arterial brachial artery pressure best represents the aortic diastolic pressure in patients with isolated systolic hypertension is not known. The problem of diastolic blood pressure measurement may explain some of the controversy surrounding the J curve.

When cuff pressures are used, the best risk predictor at present seems to be elevated systolic pressure plus a normal or low diastolic pressure: that is, a wide pulse pressure. However, at every given systolic pressure, a lower diastolic pressure carries greater cardiovascular risk, and the problem of a therapeutically reduced diastolic pressure, especially in patients with coronary heart disease, persists. Routine catheter measurements of aortic diastolic pressure in adequate numbers of patients with isolated systolic hypertension is impractical, but a calculated aortic pressure from applanated carotid or radial pulses may supply some answers. In the meantime, the elevated systolic pressure in isolated systolic hypertension requires therapy, but large reductions in cuff diastolic pressures, especially in patients with known coronary heart disease, should probably be avoided.

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